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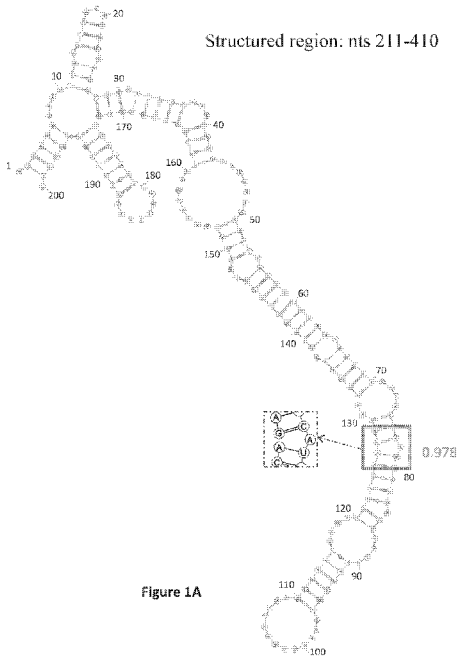

Figure 1A

(57) Abstract: The present disclosure provides small molecule compounds of Formulas I, II, and specifically of Formulas I, II- VII, and uses thereof in the inhibition and/or reduction of at least two metastatic properties of a cell. The present disclosure further provides therapeutic methods and uses of the disclosed compounds for treating metastatic malignant disorders.

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BROAD-SPECTRUM METASTASIS SUPPRESSING COMPOUNDS AND THERAPEUTIC USES THEREOF IN HUMAN TUMORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the filing date of U.S. Provisional Application No. 63/193,810, filed May 27, 2021, the entire contents of which are incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

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This invention was made with government support under grant numbers R01 CA249180 and R01 GM097455, awarded by the National Institutes of Health. The government has certain rights in the invention."

FIELD OF THE INVENTION

The invention relates to cancer therapy. More specifically, the invention relates to small molecule imidazole derivatives that inhibit metastasis-cell invasion and cell migration and to uses thereof in the treatment of human tumors.

BACKGROUND ART

References considered relevant as background to the presently disclosed subject matter are listed below:

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BACKGROUND OF THE INVENTION

One of the most unexpected findings of the genomics area is the extensive transcription of RNA from non-protein coding regions of the genome. Large-scale sequencing of human cDNA libraries elucidated tens of thousands of noncoding RNAs (ncRNAs). Prominent among this newly identified group being noncoding RNAs longer than 200 bp, the lncRNAs. The FANTOM CAT database of human lncRNAs with accurate 5' ends currently contain 26,916 lncRNAs, out of which 19,175 are potentially functional. The LNCIPEDIA database in turn has currently 127,802 human lncRNAs encoded by 56,946 genes. As of June 2018, 1867 human lncRNAs have experimental evidence to be functional. Thus, the function of the vast majority of the lncRNAs has not been

investigated yet. Recently, growing evidence indicate that lncRNAs are involved in tumorigenesis by imposing aberrant expression in cancer cells in comparison to healthy tissue cells (Morris and Mattick, 2014; Zhang and Tang, 2018). Two early on examples has to do with the tumour suppressors p15 and p21 and their promoters' spanning antisense lncRNAs (p15-as; p21-as). Ectopic expression of siRNAs against the natural promoter spanning antisense lncRNAs of p15 and p21, have reactivated these transcriptionally silenced tumour suppressor genes, which indicates oncogenic features of these antisense lncRNAs (Morris et al., 2008; Yu et al., 2008). These latter results point toward the potential of promoter-directed shRNAs to activate gene expression of tumour/metastasis suppressor genes silenced by promoter spanning as-lncRNAs. These bi-directional promoters are associated among others with neuronal functions, regulation of tumour suppressors and oncogenes.

Two other prominent examples of breast cancer linked lncRNAs are represented by HOTAIR and MALAT1. HOTAIR is a lncRNA acting as a scaffold molecule by interacting with a chromatin modification complex that enables the HOXD gene silencing in trans. In primary and metastatic breast cancer cells, the HOTAIR level is up to hundreds fold higher than in normal breast epithelia. This leads to transcription silencing of metastasis suppressor genes and results in tumor metastasis (Zhang and Tang, 2018). The MALAT1 (Metastasis-associated lung adenocarcinoma transcript 1), an evolutionary conserved, abundant nuclear lncRNA promotes cancer cell proliferation and metastasis in non-small cell lung carcinoma (Zhang and Tang, 2018).

The KAI1 metastasis suppressor gene (also known as CD82 or Tspan27), is located on human chromosome 11p11.2 and encodes for a 267 amino acid transmembrane protein that belongs to the tetraspanin family. According to the Ensemble gene browser, the KAI1 transcript can be found in 14 splice variants of which only the main variant leads to translation of the functional protein. Numerous in vitro studies have shown that KAI1 overexpression inhibits cell motility and invasion (Feng et al., 2015). A direct correlation of overall patients' survival and KAI1 expression had been observed in at least the following five solid tumours: colorectal carcinoma, gastric carcinoma, non-small cell lung cancer (NSCLC), breast cancer, and laryngeal squamous cell carcinoma (LSCC) (reviewed in Zhu et al., 2017). Likewise, at least 10 other human solid tumours are deficient in KAI1/CD82 metastasis suppressor gene expression: hepatocellular carcinoma, clear cell renal cell carcinoma, melanoma, osteosarcoma, pancreatic

carcinoma, prostate cancer, ovarian cancer, bladder carcinoma, cervical carcinoma, and thyroid cancer (Feng et al., 2015; Zhu et al., 2017). Noteworthy, in at least three solid tumours (gastric, cervical, and ovarian cancers) KAI1 affects not only tumour metastasis but also tumour proliferation (Feng et al., 2015). At the transcriptional level KAI1 is upregulated by several transcription factors such as AP2, p53, JunB, and ΔNp63α (Feng et al., 2015). Post transcriptionally, in liver HCC cells and gastric-stomach cancer KAI1 is negatively regulated by miR-197. Similarly, miR-338-5p negatively regulate KAI1 RNA in melanoma A375 cells, while miR-217 suppresses KAI1 expression in NSCLC. Loss of heterozygosity (LOH) of KAI1 in human cancers is a rare event, and similarly no point mutations were found in the KAI1 gene in human malignancies (Feng et al., 2015). Thus, clearly KAI1 expression in human tumours is being epigenetically silenced. The promotion of homotypic cell-cell adhesion is an important metastasis suppressive function of KAI1. Tumor cells must detach from the cell mass in order to invade adjacent tissue. The ability to invade is associated with the transition of cell-cell and cell-ECM adhesion molecules. It has been suggested that KAI1 has the ability to reorganize the assembly of membrane proteins and molecular concentration of integrins, which modulate the adhesive strength of the cell and promotes cell aggregation (Feng et al., 2015). In high-grade prostate cancer cells, it has been shown how up regulation of the primary fibronectin receptor α5 integrin restores the fibronectin matrix assembly, leading to increased cell cohesion and impeded detachment of the cells from the primary tumor. Moreover, recent reports propose a combination of altered KAI1-protein interactions and signaling pathways. It has been suggested that KAI1 interacts directly with the epidermal growth factor receptor (EGFR) which weakens migration signaling by rapid desensitization of EGF-induced signals (Feng et al., 2015). In addition, the actin cytoskeleton organizing FAK-Lyn-$p130^{CAS}$-CrkII pathway is attenuated by KAI1 mediated inhibition of the active $p130^{CAS}$-CrkII complex formation. As a metastasis suppressor, KAI1 has not only the task to suppress cell motility but also to prevent invasion of tumor cells by inactivating proteases that degrade the extracellular matrix. KAI1 causes a redistribution of urokinase plasminogen activator surface receptor (uPAR) and α5β1 integrins. This redistribution results in macromolecular assemblies that prevent uPAR from binding its ligand urokinase-type plasminogen activator (uPA) and subsequently in a reduced ECM proteolysis.

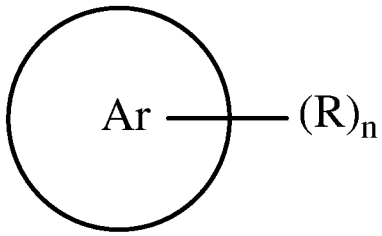
As outlined above growing evidence indicates that lncRNAs are involved in tumorigenesis by imposing aberrant expression in cancer cells in comparison to healthy tissue cells (Morris and Mattick, 2014; Zhang and Tang, 2018). In order to try identifying new breast cancer affecting lncRNA(s), the inventors established a primer-specific RT-PCR screening process for promoter-spanning lncRNAs of antisense orientation. For that purpose, total cellular RNA/nuclear RNA from three different TNBC cell lines, (MDA-MB 231, Hs578T and SUM149PT) were subject to RT-PCR with primers specific for potential upstream promoter-spanning antisense RNAs for ten of the most important human breast metastasis suppressors- and tumour suppressor-genes (Maspin, CST6, RAR-β, SYK, MAL, VGF, OGDHL, KIF1A, FKBP4, KAI1/CD82). Noteworthy, out of these 10 tested genes only one, KAI1/CD82, had an antisense lncRNA spanning its promoter and suppressing it in the triple-negative breast cancer cell line MDA-MB-231 cell line. The existence of a KAI1 antisense lncRNA that is transcribed off the KAI1/CD82 promoter imply the latter is a bidirectional promoter, which was previously reported by the inventors (Aram et al., 2017). As previously reported by the inventors, the KAI1 as-lncRNA is not polyadenylated, and is primarily present in the nucleus. Moreover, specific degradation of this lncRNA via RNAi (with either constitutive or inducible shRNAs expression) in breast cancer cells or melanoma cells led to a drop in this lncRNA and increase in KAI1 RNA and protein level in both breast cancer MDA-MB-231 and MDA-MB-435 melanoma cells. This leads to increase in cell adherence and consequently inhibition of cancer cell invasiveness, as well as inhibition of cell migration (Tzadok et al., 2013; Aram et al., 2017). Therefore, this lncRNA is a natural suppressor of KAI1 and consequently an enhancer of the metastasis process. Accordingly, the inventors named it SKAI1BC-"Suppressor of KAI1 in Breast Cancer". Sequencing of this lncRNA showed that it is 792 bp long (Aram et al., 2017). An identical sequence of a human long noncoding RNA of 792 bases (without a 3' polyA tail) derived from a cDNA library of the GM12878 cell line, contig_343318, was then found to be deposited in the UCSC database as UCSC Accession no. wgEncodeEH000148. One of many thousands of transcripts derived off this cell line. However, no other information was reported about this RNA transcript. A previous publication by the inventors, WO 2018/092137, discloses nucleic acid-based modulators of KAI1 as-lncRNA that effectively inhibit tumor cell invasiveness, migration and cell motility.

How to disrupt the oncogenic activity of the SKAI1BC lncRNA? Oligonucleotides (modified and non-modified) in the form of ASO, siRNA or shRNA are the most commonly used agents to target RNA. This is because of their ease of design using Watson-Crick base-pairing rules. However, despite numerous attempts over the past 41 years (oligonucleotides), and 22 years (RNAi based technologies), the FDA approved only nine ASOs/siRNAs as drugs until 1/2020. Therefore, there is need in the art to provide bioactive small molecules that bind and ablate the oncogenic activity of SKAI1BC lncRNA. A method to predict small compounds binding to RNAs has been previously developed by one of the inventors (Velagapudi et al., 2014; Disney et al., 2016). They have successfully used this approach to identify small molecules that target expanded repeating RNAs, which cause or contribute to neurological/neuromuscular diseases , as well as small compounds that target oncogenic pre-miRNAs and viral RNA (Velagapudi et al., 2014; Costales et al., 2018; Haniff et al., 2020). Overall the scientific community has until now tried to inhibit 25 disease causing RNAs (via 11 pre-miRs, 7 tandem repeats RNAs, 3 pre-mRNAs, 2 mRNAs, 2 lncRNAs), with 42 different small molecules (Meyer et al., 2020; Haniff et al., 2020). FDA has so far approved one compound (ridisplam, PTC/Roche) as a drug, and another small molecule (branaplam, Novartis) is in phase II clinical trials (Meyer et al., 2020).

There is need in the art to provide effective compounds for inhibiting metastatic properties of cancer cells.

SUMMARY OF THE INVENTION

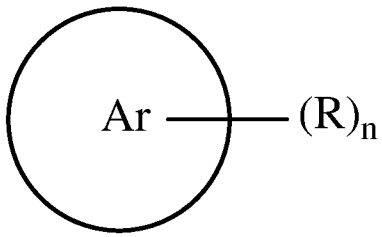
In a first aspect, the invention relates to a method for the inhibition and/or reduction of at least one metastatic property of a cell. More specifically, the method comprising the step of contacting the cell with an inhibitory effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or with any vehicle, matrix, nano-, micro-particles thereof. In some specific embodiments, **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of the R may be the same or different.

In another aspect, the present invention relates to an inhibitory effective amount of at least one small molecule compound for use in a method that results in the inhibition and/or reduction of at least one metastatic property of a cell. In some embodiments, the compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof. More specifically, **Formula I** is:

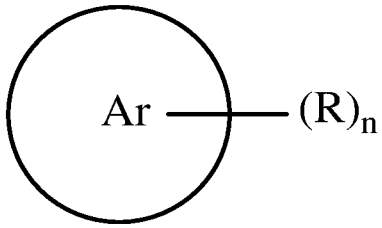


Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In yet another aspect thereof, the present invention provides methods of inhibiting and/or reducing a metastatic process in a subject in need thereof. More specifically, the method comprising the step of administering to the subject a therapeutically effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any

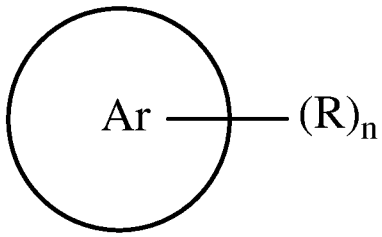
vehicle, matrix, nano-, micro-particles thereof, any combinations thereof, or any composition thereof. In some embodiments, **Formula I** is



Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

Another aspect of the present invention relates to an inhibitory effective amount of at least one small molecule compound for use in a method of inhibiting and/or reducing a metastatic process in a subject in need thereof. In some embodiments, the compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any compositions thereof. More specifically, **Formula I** is:

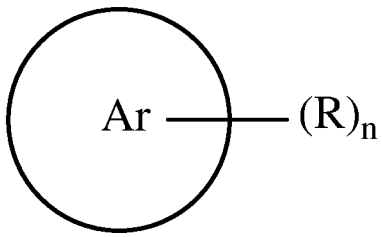


Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In another aspect, the present disclosure provides a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject. More specifically, the method comprises the

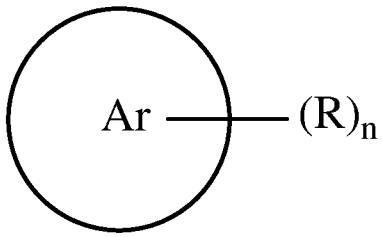
step of administering to the subject a therapeutically effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof, or any composition thereof. More specifically, **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In another aspect, the present invention provides an inhibitory effective amount of at least one small molecule compound for use in a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject. In some embodiments, the compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof. More specifically, **Formula I** is:

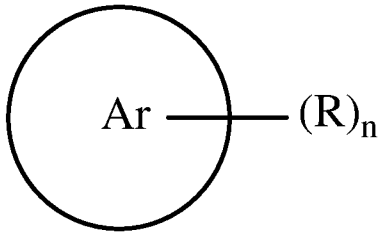


Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be

independently further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

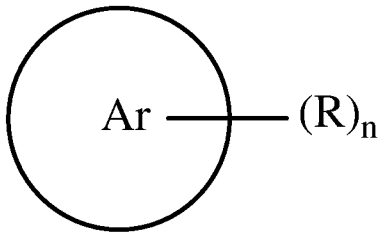
In another aspect, the present invention relates to a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject treated with at least one anti-proliferative therapy. More specifically, the method comprises the step of administering to the subject a therapeutically effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof, or any composition thereof, prior to, after, and/or simultaneously with the at least one anti-proliferative therapy. In some embodiments, **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

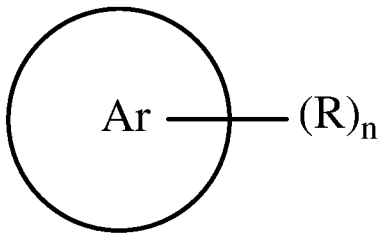
In another aspect the present invention provides an inhibitory effective amount of at least one small molecule compound for use in a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject treated with at least one anti-proliferative therapy. In some embodiments, said compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any compositions thereof, and wherein said **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In yet another aspect the present invention provides a method for modulating the activity, levels and/or stability of at least one antisense long non-coding RNA of the metastasis suppressor gene KAI1/cluster of differentiation 82 (CD82) (KAI1 as-lncRNA, suppressor of KAI1 in breast cancer (SKAIBC)), in a cell. In some embodiments the method comprising the step of contacting said cell with a modulatory effective amount of at least one small molecule compound of **Formula II**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or with any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any composition thereof, wherein said **Formula II** is:



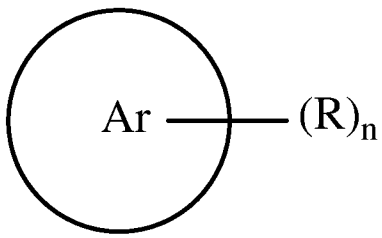
Formula II

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is a dihydroimidazole derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10, wherein when n>1, any one of said R may be the same or different, and wherein said KAI1 as-lncRNA has a length of about

700 to about 1000 nucleotides and is encoded upstream of the KAI1/CD82 gene transcription start site (TSS) in an antisense orientation, specifically, the major TSS.

It is noted that the compound of **Formula II** is within the scope of the compound of **Formula I**. Specifically, the compound of **Formula II** is limited to R being a dihydroimidazole derivative. Thus, aspects and embodiments detailed herein above and below in connection with the compound of **Formula I** are applicable *mutatis-mutandis* to the compound of **Formula II**.

In another aspect of the present disclosure at least one small molecule compound of **Formula II**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof, for use in a method for modulating the levels and/or stability of at least one antisense long non-coding RNA of the metastasis suppressor gene KAI1/cluster of differentiation 82 (CD82) (KAI1 as-lncRNA, suppressor of KAI1 in breast cancer (SKAIBC)), in a cell, wherein said **Formula II** is:



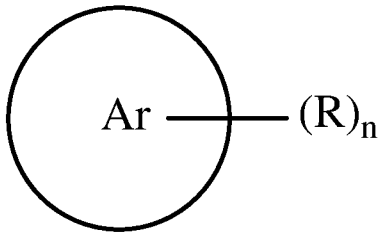
Formula II

wherein in some embodiments, Ar is an aromatic or heteroaromatic moiety; wherein R is a dihydroimidazole derivative;

wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10; wherein when n>1, any one of said R may be the same or different, and wherein said KAI1 as-lncRNA has a length of about 700 to about 1000 nucleotides and is encoded upstream of the KAI1/CD82 gene transcription start site (TSS) in an antisense orientation, and wherein said KAI1 as-lncRNA has a length of about 700 to about 1000 nucleotides and is encoded upstream of the KAI1/CD82 gene transcription start site (TSS) in an antisense orientation.

In another aspect the present invention provides at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or

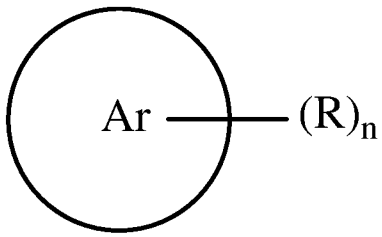
with any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any composition thereof, wherein said **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of the R may be the same or different, provided that said at least one small molecule compound of **Formula I** is not any one of compounds #1, #2, #3, #4, #5 and #6, also disclosed herein as compounds of Formulas IV, III, V, VI, VIII and VII, respectively.

In another aspect the present invention provides at least one small molecule compound of **Formula II**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any conjugates thereof, or with any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any composition thereof, wherein said **Formula II** is:



Formula II

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is a dihydroimidazole derivative; wherein each of said Ar and R may optionally be independently further substituted; wherein n is an integer from 1 to 10, wherein when n>1, any one of said R may be the same or different, provided that said at least one small molecule compound of

Formula II is not any one of compounds #1, #2, #3, #4 and #5, also disclosed herein as compounds of Formulas IV, III, V, VI and VIII, respectively.

Yet, in a further aspect, the present invention provides a composition comprising at least one compound of the present disclosure, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof. The compositions of the present disclosure may optionally further comprise at least one pharmaceutically acceptable carrier/s, excipient/s, auxiliaries, and/or diluent/s.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to better understand the subject matter that is disclosed herein and to exemplify how it may be carried out in practice, embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Figure 1A-1D: ***Predicted structures in the SKAI)1BC lncRNA***

Boxed regions represent probabilities of predicted loop targets in the structure and are color coded as follows: (------) represents 50% > Probability, (··········) represents 60% > Probability ≥ 50%; (·····) represents 90% > Probability ≥ 80%; and (. . . . .) represents 99% > Probability ≥ 95%.

Fig. 1A. shows the structured region of nucleotides 211-410;

Fig. 1B. shows the structured region of nucleotides 341-500;

Fig. 1C. shows the structured region of nucleotides 381-640;

Fig. 1D. shows the structured region of nucleotides 611-790.

Figure 2: ***Top Inforna hits for SKAI1BC RNA structures and their fitness scores***. Only shown are structures for the indicated regions with Inforna hits whose fitness scores were at least 70%. Probabilities of predicted loop targets in structures are color coded as follows: (------) represents 50% > Probability, (··········) represents 60% > Probability ≥ 50%; (·····) represents 90% > Probability ≥ 80%; and (. . . . .) represents 99% > Probability ≥ 95%. The figure further depicts the structures of compounds #1, #2, #3, #4 and #5, also disclosed herein as compounds of Formulas IV, III, V, VI and VIII, respectively), for each of the specified structured regions.

Fig. 2A. shows hits for structured region of nucleotides 211-410;

Fig. 2B. shows hits for structured region of nucleotides 341-500;

Fig. 2C. shows hits for structured region of nucleotides 381-640;

Fig. 2D. shows hits for structured region of nucleotides 611-790.

Figure 3A(i-iii)-3B(i-iii): ***Compounds effect on cell invasion, cell migration and KAI1/CD82 RNA level of TNBC cell lines***

Fig. 3A (i-iii): MDA-MB-231 and BT-549 cell lines.

Fig. 3B (i-iii): Hs578T and HCC70 cell lines.

Cells were treated with 5μM of each of the compounds (#1, #2, #3, #4 and #6, also disclosed herein as Formulas IV, III, V, VI and VII, respectively). **Effect on KAI1 RNA level** (upper rows**, 3A(i), 3B(i)**): Cells were treated with the compounds for 48h. Relative KAI1 mRNA Expression was quantified by RT followed by Real-Time PCR with HMBS as endogenous control. **Effect on Cell Invasion and Migration** (middle and lower rows, **3A(ii), 3B(ii) and 3A(iii), 3B(iii),** respectively)**:** Cells were treated with the compounds for 24h and then seeded for additional 24h while under starvation conditions and in the presence of the compounds either in CytoSelect (Cell Biolabs) transwell chambers for cell invasion assay or in ThinCert™ (Greiner Bio-One) inserts for cell migration assay. Cells' invasion or migration from the upper chamber to the chemoattractant (10% serum) in the lower chamber were quantified using colorimetric assay.

Figure 4 (i-iii): Compounds effect on breast cancer cells' invasion, migration and ***KAI1/CD82 RNA***

MCF-7 (Luminal A), ZR-75-30 (Luminal B) and SkBr3 (HER2+) were treated with 5μM of each of the compounds (#1, #2, #3, #4 and #6, also disclosed herein as Formulas IV, III, V, VI and VII, respectively). **Effect on KAI1 RNA level** (upper row, **4(i)**): Cells were treated with the compounds for 48h. Relative KAI1 RNA Expression was quantified by RT followed by Real-Time PCR with HMBS as endogenous control. **Effect on Cell Invasion and Migration** (middle and lower rows, **4(ii), 4(iii),** respectively)**:** Cells were treated with the compounds for 24h and then seeded for additional 24h while under starvation conditions and in the presence of the compounds either in CytoSelect (Cell Biolabs) transwell chambers for invasion assay or in ThinCert™ (Greiner Bio-One) inserts for migration assay. Cells invasion or migration from the upper chamber to the chemoattractant (10% serum) in the lower chamber were quantified using colorimetric assay.

Figure 5 (i-iii): ***Compounds effect on cell invasion, cell migration and KAI1/CD82 RNA level of Melanoma cell lines***

SKMEL-24, RPMI-7951 and MDA-MB-435 cells were treated with 5µM of each of the compounds (#1, #2, #3, #4 and #6, also disclosed herein as Formulas IV, III, V, VI and VII, respectively). **Effect on KAI1 RNA level** (upper row, **5(i)**): Cells were treated with the compounds for 48h. Relative KAI1 RNA Expression was quantified by RT followed by Real-Time PCR with HMBS as endogenous control. **Effect on Cell Invasion and Migration** (middle and lower rows, **5(ii), 5(iii),** respectively): Cells were treated with the compounds for 24h and then seeded for additional 24h while under starvation conditions and in the presence of the compounds either in CytoSelect (Cell Biolabs) transwell chambers for invasion assay or in ThinCert™ (Greiner Bio-One) inserts for migration assay. Cells invasion or migration from the upper chamber to the chemoattractant (10% serum) in the lower chamber were quantified using colorimetric assay.

Figure 6 (i-iii): ***Compounds effect on cell invasion, cell migration and KAI1/CD82 RNA level of pancreatic cancer cell lines***

AsPC-1, BxPC-3 and CFPAC-1 cells were treated with 5µM of each of the compounds (#1, #2, #3, #4 and #6, also disclosed herein as Formulas IV, III, V, VI and VII, respectively). **Effect on KAI1 RNA level** (upper row**, 6(i)**): Cells were treated with the compounds for 48h. Relative KAI1 mRNA Expression was quantified by RT followed by Real-Time PCR with HMBS as endogenous control. **Effect on Cell Invasion and Migration** (middle and lower rows, **6(ii), 6(iii),** respectively): Cells were treated with the compounds for 24h and then seeded for additional 24h while under starvation conditions and in the presence of the compounds, either in CytoSelect (Cell Biolabs) transwell chambers for invasion assay or in ThinCert™ (Greiner Bio-One) inserts for migration assay. Cells invasion or migration from the upper chamber to the chemoattractant (10% serum) in the lower chamber were quantified using colorimetric assay.

Figure 7A(i-iii)-7B(i-iii): ***Compounds effect on cell invasion, cell migration and KAI1/CD82 RNA level of NSCLC cell lines***

Fig. 7A (i-iii): A-549 and NCI-H1975 cell lines.

Fig. 7B(i-iii): NCI-H1299 and NCI-H2030 cell lines.

Cells were treated with 5µM of each of the compounds (#1, #2, #3, #4 and #6, also

disclosed herein as Formulas IV, III, V, VI and VII, respectively). **Effect on KAI1 RNA level** (upper rows, **7A(i), 7B(i)**): cells were treated with the compounds for 48h. Relative KAI1 RNA Expression was quantified by RT followed by Real-Time PCR with HMBS as endogenous control. **Effect on Cell Invasion and Migration** (middle and lower rows, **7A(ii), 7B(ii),** and **7A(iii), 7B(iii)**, respectively): Cells were treated with the compounds for 24h and then seeded for additional 24h while under starvation conditions and in the presence of the compounds, either in CytoSelect (Cell Biolabs) transwell chambers for invasion assay or in ThinCert™ (Greiner Bio-One) inserts for migration assay. Cells invasion or migration from the upper chamber to the chemoattractant (10% serum) in the lower chamber were quantified using colorimetric assay.

Figure 8 (i-iii): ***Compounds effect on cell invasion, cell migration and KAI1/CD82 RNA level of liver carcinoma cell lines***

SK-HEP1 and C3A cell lines were treated with 5μM of each of the compounds (#1, #2, #3, #4 and #6, also disclosed herein as Formulas IV, III, V, VI and VII, respectively). **Effect on KAI1 RNA level** (upper row, **8(i)**): Cells were treated with the compounds for 48h. Relative KAI1 mRNA Expression was quantified by RT followed by Real-Time PCR with HMBS as endogenous control. **Effect on Cell Invasion and Migration** (middle and lower rows, **8(ii) and 8(iii),** respectively): Cells were treated with the compounds for 24h and then seeded for additional 24h while under starvation conditions and in the presence of the compounds, either in CytoSelect (Cell Biolabs) transwell chambers for invasion assay or in ThinCert™ (Greiner Bio-One) inserts for migration assay. Cells invasion or migration from the upper chamber to the chemoattractant (10% serum) in the lower chamber were quantified using colorimetric assay.

Figure 9A-9B: ***Compounds effect on TNBC cell lines Proliferation***

MDA-MB-231 **(Fig. 9A)**, and BT549 **(Fig. 9B)** cells were counted and seeded evenly into 6-well plates. The cells were incubated with the medium alone or with the addition of 5uM of the different compounds. After 48 h of incubation, the cells were harvested and counted again to assess cell proliferation. Data are presented as the mean +/- standard error of the mean of three independent experiments.

Figure 10A-10C: ***Compounds effect on breast cancer cell lines Proliferation***

MCF-7 **(Fig. 10A)**, ZR-75-30 **(Fig. 10B)** and SkBr3 **(Fig. 10C)** cells were counted and seeded evenly into 6-well plates. The cells were incubated with the medium alone or with the addition of 5uM of the different compounds. After 48 h of incubation, the cells were harvested and counted again to assess cell proliferation. Data are presented as the mean +/- standard error of the mean of three independent experiments.

Figure 11A-11B: ***Compounds effect on Melanoma cell lines Proliferation***

SKMEL-24 **(Fig. 11A)** and RPMI-7951 **(Fig. 11B)** cells were counted and seeded evenly into 6-well plates. The cells were incubated with the medium alone or with the addition of 5uM of the different compounds. After 48 h of incubation, the cells were harvested and counted again to assess cell proliferation. Data are presented as the mean +/- standard error of the mean of three independent experiments.

Figure 12A-12B: ***Compounds effect on pancreatic cancer cell lines Proliferation***

AsPC-1 **(Fig. 12A)** and CFPAC-1 **(Fig. 12B)** cells were counted and seeded evenly into 6-well plates. The cells were incubated with the medium alone or with the addition of 5uM of the different compounds. After 48 h of incubation, the cells were harvested and counted again to assess cell proliferation. Data are presented as the mean +/- standard error of the mean of three independent experiments.

Figure 13A-13B: ***Compounds effect on NSCLC cell lines Proliferation.***

NCI-H1299 **(Fig. 13A)** and NCI-H2030 **(Fig. 13B)** cells were counted and seeded evenly into 6-well plates. The cells were incubated with the medium alone or with the addition of 5uM of the different compounds. After 48 h of incubation, the cells were harvested and counted again to assess cell proliferation. Data are presented as the mean +/- standard error of the mean of three independent experiments.

Figure 14A-14B: ***Compounds effect on liver cancer cell lines Proliferation***

SK-HEP1 **(Fig. 14A)**, and C3A **(Fig. 14B)** cells were counted and seeded evenly into a 6-well plate. The cells were incubated with the medium alone or with the addition of 5uM of the different compounds. After 48 h of incubation the cells were harvested and counted again to assess cell proliferation. Data are presented as the mean +/- standard error of the mean.

DETAILED DESCRIPTION OF THE INVENTION

One of the acute problems in cancer therapy is the scarcity of effective drugs against metastasis, resulting in a situation where 90% of the cancer death results from metastasis. Another major difficulty emerging in cancer therapy is the recent realization that many of the ~30,000 unexplored human lncRNAs are functional, and a good many likely to be involved in malignancy. The inventor's recent discovery of a novel human lncRNA, which was initially identified as a suppressor of the KAI1/CD82 in triple-negative breast cancer, confronted the inventors with the question how to stimulate the epigenetically suppressed activity of KAI1 in metastatic cancer/s. This is a challenging problem because the KAI1/CD82 metastasis suppressor is known to be epigenetically silenced in at least 15 solid human tumors, and possibly in a few hematopoietic human malignancies as well. Importantly, the level of KAI1 expression is prognostic of overall survival or other clinical key features of the patients' disease in at least 10 solid human cancers. Using a program that predict, via free energy minimization, the secondary structure of the lncRNA (RNAfold from the ViennaRNA package), four regions that are the most probable to be folded into targetable structures were identified (nts 211-410; nts 341-500; nts 381-640; nts 611-790; **Fig. 1A, 1B, 1C, 1D**, respectively) within the SKAI1BC lncRNA (also denoted by SEQ ID NO: 1), by one of the inventors (Prof. Disney). The nts 381-640 region is the most stable with $\Delta G^\circ = -112.9$ kcal (**Fig. 1C**). These presumably targetable small structures were compared to the RNA motifs-small molecule interactions InfoRNA 2.0 database, which was generated experimentally primarily by Disney's group (Disney et al., 2016). This led to identification of five compounds (#1-#5, also denoted by **Formulas IV, III, V, VI,** and **VIII**) that were suggested to bind the human SKAI1BC lncRNA with a fitness score of at least 70% for each region (**Fig. 2**). For example, the 5′CAU/3′G_A, 5′CUC/3′G_G, 5′GUC/3′C_G, 5′GCG/3′C_C, bulge loops (**Figs. 2A**, **2B, 2C, 2D,** respectively) in these regions were predicted to bind to a similar set of compounds with fitness scores up to 100%, indicating that a particular compound may be able to inhibit multiple sites on the lncRNA. Obviously, the inventors seek for compounds that not only bind the SKAI1BC as-lncRNA, but also inhibit its activity as might be reflected in KAI1 stimulation. Therefore, these compounds were first assayed for stimulation of KAI1 RNA level in the triple negative breast cancer (TNBC) cells. The inventors found that at least 4 out of these 5 compounds (designated herein as compounds #1-#4, of Formulas IV, III, V, and

VI, respectively), at 5uM stimulated KAI1 RNA expression by up to 2.1-2.2-fold in the TNBC MDA-MB-231, and BT-549 cell lines (**Fig. 3A** top row **3A(i)**). Compound #5 had low activity, and therefore was not tested further (**data not shown**). The negative control MCF10A cell line that does not metastasize did not respond at all with regard to KAI1 RNA stimulation (**data not shown**). Compound #6 (also referred to herein as the compound of Formula VII), which belongs to a different chemical group and was not predicted to bind the KAI1 as lncRNA, did not stimulate KAI1 RNA level in these four TNBC cell lines. Importantly, incubation of these five compounds (#1-#4 & #6) at 5uM for 48 hours with each of the four TNBC cell lines resulted in significant inhibition of metastasis cell invasion typically from 64%-94% (**Fig. 3A (ii)** and **3B (ii)** middle rows). Interestingly, compound #6 inhibited cell invasion of all four TNBC cell lines, even though their KAI1 RNA was not boosted by compound #6 treatment (**Fig. 3A(ii)** and **3B (ii)** middle rows). In contrast, none of the five compounds inhibited the modest invasion of the MCF10A derived cells (data not shown). These experiments were followed by inquiry of the compounds effect on cell migration, the second step of metastasis following cell invasion. As shown (**Fig. 3A (iii)** and **3B (iii),** bottom rows), all four tested TNBC cell lines (MDA-MB-231, BT-549, Hs578T and HCC70) had their cell migration inhibited by each of the five said compounds (from 30%-89%). These initial results led the inventors to test three non-TNBC breast cancer cell lines: MCF-7 representing Luminal A, ZR-75-30 belonging to Luminal B, and SkBr3 reflecting the HER2 overexpressing group. All three cell lines were inhibited in metastasis cell invasion and migration by all five compounds; The partial stimulation of KAI1 RNA by these five compounds had been marginal (**Fig. 4 (i),** top row).

The profound metastasis inhibition of breast cancer cells in culture has stimulated the inventors to test these five compounds further in established cell lines derived from Melanoma, Pancreatic carcinoma, NSCLC, and Liver hepatocellular carcinoma patients. Accordingly, human tumor cell lines of these four malignancies were obtained from the ATCC and tested as outlined above for their response to the compounds of the present disclosure in terms of KAI1 RNA stimulation, metastasis cell invasion, and metastasis cell migration. In Melanoma SK-MEL-24, MDA-MB-435 cell lines (**Fig. 5 (i),** top row) there are significant stimulations of KAI1 RNA levels by almost all five compounds, including compound #6 (Formula VII). However, actually almost without exception, there are no KAI1 RNA stimulations in Melanoma RPMI-7951 (**Fig. 5 (i),** top row).

Yet, the five compounds manage to inhibit the cell invasion in the three Melanoma cell lines including RPMI-7951 (**Fig 5 (ii),** middle row). Moreover, in the three tested Melanoma cell lines, SK-MEL-24, MDA-MB-435 and RPMI-7951 (the latter despite of its non-induced KAI1 RNA) there was also cell migration inhibition triggered by all five compounds (**Fig. 5 (iii),** bottom row). The results of compound #6, and the other four compounds in the RPMI-7951 cells clearly demonstrate that inhibition of metastasis cell invasion and migration depends on the cell line, and can occur even in the absence of the metastasis suppressor KAI1 RNA stimulation (see also below).

Interestingly, concentration curve of molecule #2 (for example) in the melanoma MDA-MB-435 cells inhibited invasiveness by 81% at 5uM, and still by 23% at 50 nM; meaning a very significant cell invasion inhibition at low compound concentrations.

In contrast to the diversity exhibited by the three tested Melanoma cell lines **(Fig. 5)**, the three selected pancreatic carcinoma cell lines displayed a uniform response **(Fig. 6)**. That is to say that all five compounds enhanced KAI1 RNA levels at 5uM, triggering significant metastasis cell invasion inhibition, as well as inhibiting cell migration in all three cell lines (AsPC-1, BxPC-3, CFPAC-1 see **Fig. 6**). Another tumor tested herein is the Non-Small Cell Lung Carcinoma (NSCLC) represented by four cell lines. As it turned, depending on the cell line, all five compounds enhanced KAI1 RNA level, in one cell line or more (**Fig. 7A** and **7B**). Yet, all five compounds inhibited in all four NSCLC cell lines (A-549, NCI-H1975, NCI-H1299, NCI-H2030) both cell invasion and cell migration (**Fig. 7A(ii), (iii)** and **7B(ii), (iii),** respectively). This observation again demonstrates that there are at least two mechanisms shared by the five compounds: one, which acts via KAI1 RNA elevation, the other independent of KAI1 enhancement.

Next, the liver hepatocellular carcinoma SK-HEP1 and C3A cell lines for KAI1 RNA stimulation were tested, which turned out to be partial depending on both the specific compound and cell line (**Fig. 8**). Yet both cell lines metastasis cell invasion and migration were inhibited at 5uM by each of the five compounds, including compound #6 (Formula VII). The inventors next tested whether anyone of the five compounds has an effect on proliferation of the eight tumors derived cell lines. The experiment performed three times with every cell line, involved treating the cells with 5uM of each of the five compounds for 48 hours, as compared to the mock control sample. As one can see in **Figures 9** to **14** there are at most 9% inhibition of cell proliferation among the said eight solid tumors. Noteworthy, if there is any enhancement of cell proliferation

of the tumor cell lines it is between 1%-12%. The fact that Compound #6 (Formula VII) for example, does not enhance KAI1 RNA level in TNBC MDA-MB-231 cells, unlike Compound #3 (Formula V), and yet inhibit both cell invasion and migration of these cells, suggests the existence of alternative mechanism for the above. Therefore, these cells were treated with either 0.05% DMSO to serve as mock, and 5uM Compounds #3 or #6 for 48 hours. The effect of Compound #3 and compound #6 on gene expression pathways was tested in MDA-MB-231 TNBC cell line. Total RNA was extracted, selected for polyA RNA, reverse-transcribed to cDNA and a cDNA Libraries were prepared. Sequencing was done by NGS and Relative Gene Expression has been analyzed. From detailed studies of **Fig. 3** and KEGG gene expression pathways one concludes that Compound #3 (Formula V) is acting via KAI1/CD82 RNA enhancement, while Compound #6 (Formula VII) is not (see below).

At this point, the inventors examined the compounds effect *in vivo* on spontaneous metastasis initially in TNBC derived xenografts. For that purpose, a derivative of the TNBC, the MDA-MB-231 cell line which express a mutant Luciferase gene (MDA-MB-231-Luc2) is being used. Importantly, this cell line had been infected with the lentiviral vector TGL encoding for GFP, Firefly luciferase, and the human herpesvirus 1 TK. Therefore, metastasis development can be monitored by either bioluminescence or fluorescence measurement. These TNBC-derived tumor cells (200,000) where orthotopically injected on day1 to the fourth fat pad of the female immune-deficient BALB/cOlaHsd-Foxn1nude mice. One group of mice is receiving injected Compound #2 MTD (50 mg/kg mice), three times/week starting on day 3, for six weeks. Another group of mice is receiving 37.5 mg/kg mice injection of Compound #2 as outlined above. The third mice group is receiving injected PBS instead, serving as the experiment's reference mock. All three groups are scanned for their primary tumors' and metastases' luminescence twice a week, using both an IVIS Imager and a CT. Primary tumors and organs are being harvested, fixed in 4% paraformaldehyde, embedded in paraffin, sliced, mounted on slides and stained with H&E. That part including its analysis is being done at the Interdepartmental Core Facility of TAU Medical School. In preparation are CDXs with MDA-MB-231-Luc2 in NSG mice (Iorns et al., 2012) with Compounds #2 and #1, as well as NSCLC H1299-luc in NSG mice with each of the two indicated compounds.

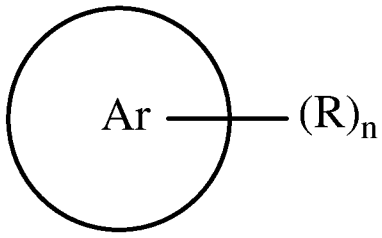
Importantly, as the proliferation tests were performed under the same compounds concentration (5uM) and incubation times (~48 hours) employed for the metastasis tests, the severe cell invasion- and migration-inhibition observed in there cannot be explained by the compounds' minor inhibition (if any) of the cells' proliferation. This may imply that *in vivo* these compounds may have little if any side effects on the neighboring normal tissue cells. Having compounds that inhibit just the metastasis process is a rare finding. These have been recently named Migrastatics (Gandalovicova et al., 2017; Cermak et al., 2020; Malques et al., 2021). This may enable its/their perhaps prolonged usage, together with specific primary tumor killing drugs, preventing metastasis dormancy activation (Risson et al., 2020).

Another important observation that was made by the present inventors being that these 48 hours incubation of anyone of the compounds at 5uM concentration does not degrade the SKAI1BC lncRNA; Quantified by RT followed by Real-Time PCR with HMBS as endogenous control (data not shown). Without being bound by the theory, the inventors assume that compounds binding to the particular SKAI1BC lncRNA prevent the lncRNA annealing to the complementary sense DNA strand (at the KAI1 promoter region), and thus enabling the KAI1 gene to be transcribed. Alternatively, the compounds may interfere with the SKAI1BC lncRNA binding of an essential KAI1 gene/s-specific transcription factor, and in this way enhance KAI1 RNA transcription. Noteworthy, about half of the cell lines from each tumor were derived from metastases, rather than from the primary tumors. Importantly, none of the said five compounds is currently being used as a drug to any disease, or claimed by any other patent. In view of the fact that until now there are very few effective anti-metastasis drugs (Gandalovicova et al., 2017; Cermak et al., 2020; Malques et al., 2021), the potential importance of these compounds, and derivatives thereof is clear. Such anti-metastasis drug/s should be given together with drug/s that kill the primary tumor cells. Moreover, such compound/s may potentially be given for prolonged periods to maintain the tumor in its dormancy state.

As discussed herein, the present disclosure relates to small molecules that inhibit solid tumors' metastasis. Five compounds have been tested and proven active in cultures of eight solid human tumors: Breast TNBC, Breast Luminal A, Breast Luminal B, Breast HER2 overexpressing, Melanoma, Pancreatic adenocarcinoma, NSCLC and Liver cancer. All, severely inhibit metastasis-cell invasion and -cell migration, while at the

same low drug concentration hardly affect cell proliferation. The metastasis-specific activities of these compounds, coupled to their lack of cytotoxicity, may also enable their use to prevent formation of disseminated tumor cells (DTCs). This is due to the recent discovery of biomarkers for generation of DTCs (Sauer S et al., 2021). Obviously, such intervention is likely to be desirable in human tumors developing metastases early on after primary tumors' formation. Disclosed are two types of lead compounds which depending on the cell line, one type (such as Compounds #1-#4, Formulas IV, III, V, VI, respectively) for the most part enhances the expression of the human KAI1/CD82 metastasis suppressor gene (probably via binding the SKAI1BC lncRNA). Yet, none of Compounds #1-#4 enhance Breast SkBr3 cells (**Fig. 4**). The other type, such as Compound #6 acts in TNBC cell lines by a different as yet unknown mechanism/s. Yet, in at least three pancreatic cell lines, Compound #6 (Formula VII) acts via enhancement of KAI1/CD82 RNA (**Fig. 6**). Eight additional solid cancers such as prostate, gastric, ovarian, colon, cervical, renal clear cell carcinoma, osteosarcoma, and LSCC cancers are known to be dependent on deficiency in KAI1/CD82 expression. Therefore, more tumors are likely to respond to these compound/s (Feng et al. 2015; Zhu et al., 2017).

Thus, in a first aspect, the invention relates to a method for the inhibition and/or reduction of at least one metastatic property of a cell. More specifically, the method comprising the step of contacting the cell with an inhibitory effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or with any vehicle, matrix, nano-, micro-particles thereof. In some specific embodiments, **Formula I** is:



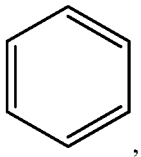
Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be

further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of the R may be the same or different.

Embodiments detailed herein below in connection with the compound of **Formula I** of the invention are applicable *mutatis-mutandis* to all aspects of the invention.
In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)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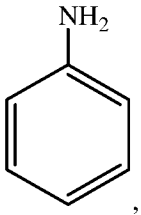
b)



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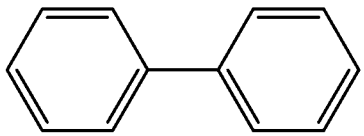
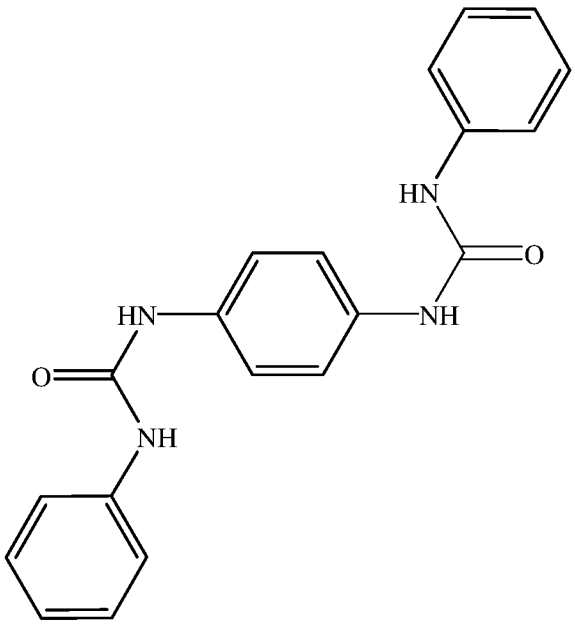
c)


, and

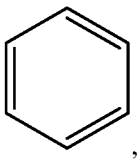
d)



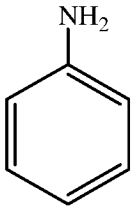
wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)

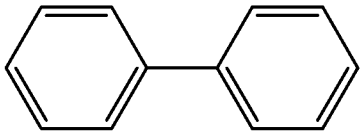

,

b)



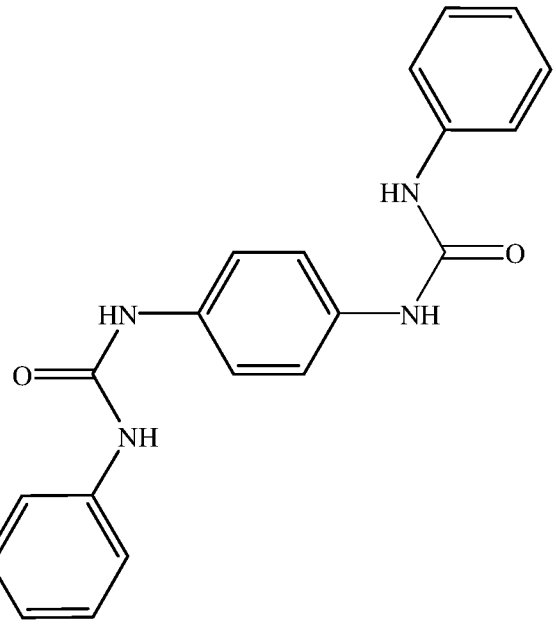
,

c)



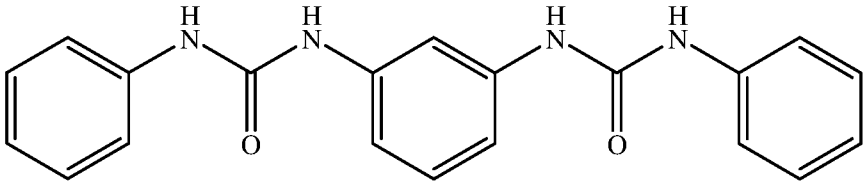
,

d)



, and

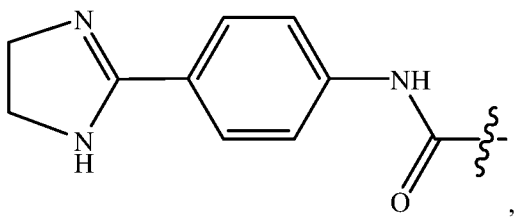
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

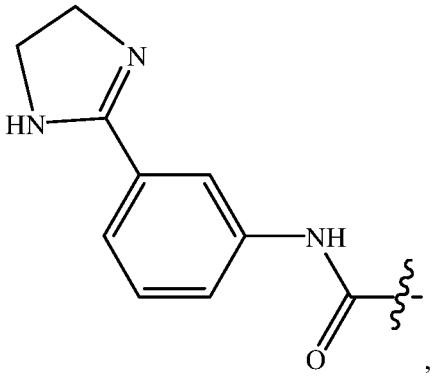
In yet some further embodiments of the method disclosed herein, the R of the at least one small molecule compound of **Formula I**, may be selected from the group consisting of:

a)



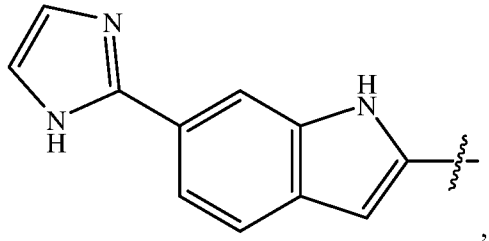
,

b)



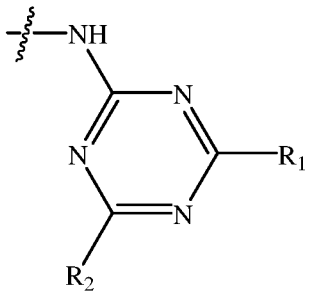
,

c)



, and

d)

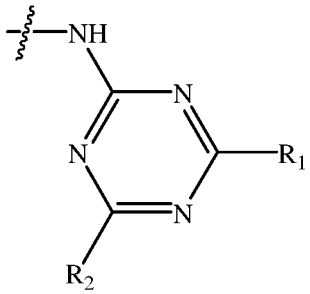


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, -NH_2, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

and wherein each of said R may optionally be further substituted.

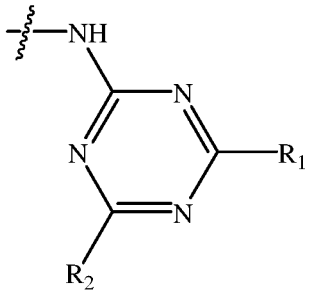
In some embodiments each of said R is not further substituted.

In some embodiments at least one of R is

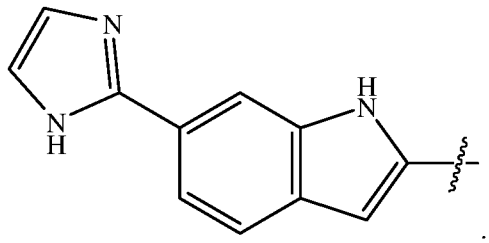


wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$. In some specific embodiments of the method of the present disclosure, at least one of the R is an imidazole derivative and a triazine derivative.

In some embodiments at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



In some specific embodiments of the method of the present disclosure, the at least one of the R is an imidazole derivative.

In some specific embodiments of the method of the present disclosure, the at least one of the R is a dihydroimidazole derivative.

In some specific embodiments of the method of the present disclosure, at least one of the R is a dihydroimidazole derivative.

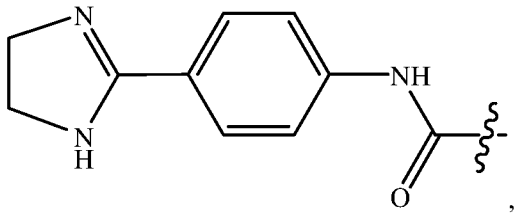
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative which may be the same or different.

In some further specific embodiments, the R of the compound used in the methods of the present disclosure, may be repeated n times. In some embodiments, n may be 2, 3, or 4.

In some specific embodiments of the method of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

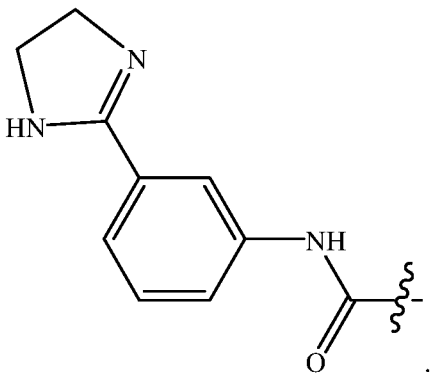
In some specific embodiments of the methods of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



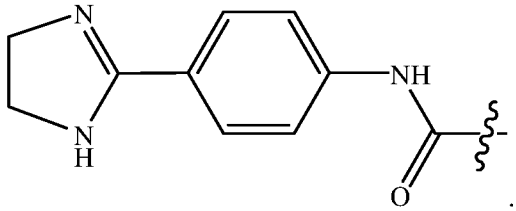
, or

b)



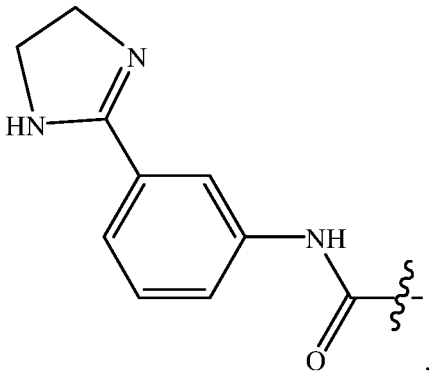
.

In some specific embodiments of the methods of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



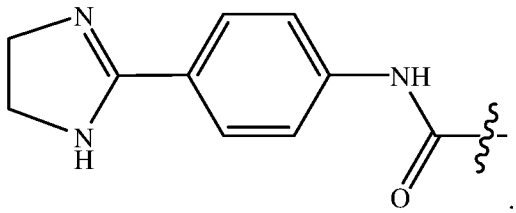
.

In some specific embodiments of the methods of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



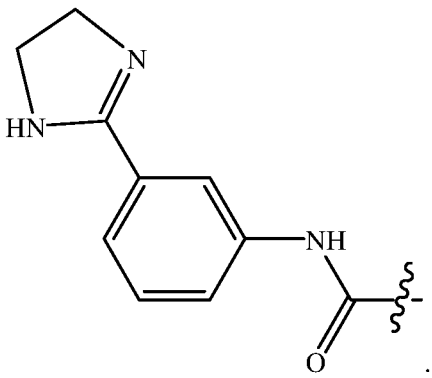
.

In some specific embodiments of the methods of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



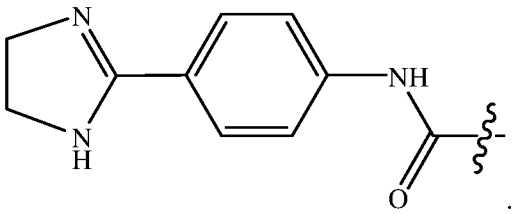
.

In some specific embodiments of the methods of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative

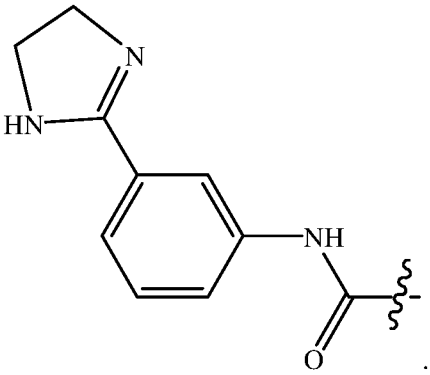


.

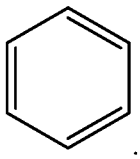
In some specific embodiments of the methods of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



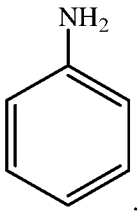
In some specific embodiments of the methods of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



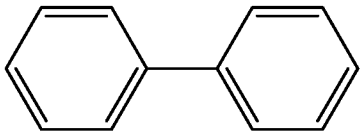
Thus, according to some embodiments, the compounds of Formula I used by the methods of the invention may comprise Ar that is:



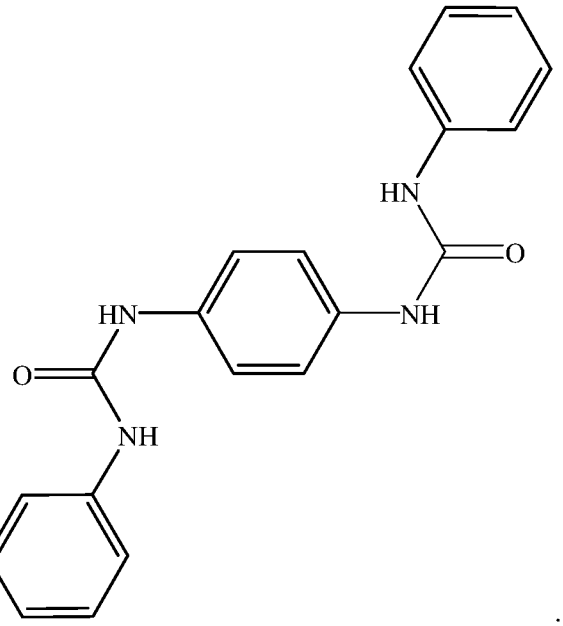
According to some further embodiments, the compounds of Formula I used by the methods of the invention may comprise Ar that is:



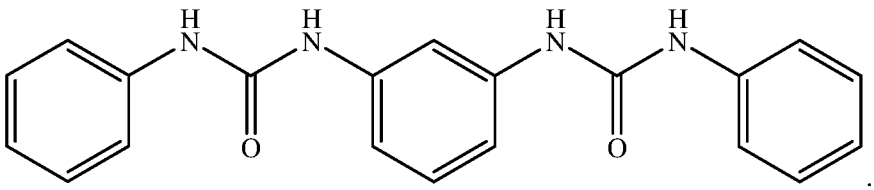
According to some embodiments, the compounds of Formula I used by the methods of the invention may comprise Ar that is:



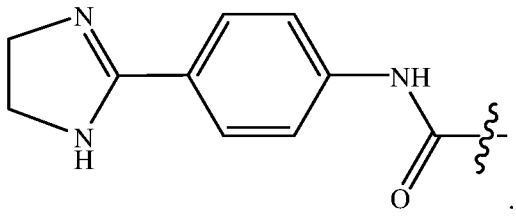
Still further, according to some embodiments, the compounds of Formula I used by the methods of the invention may comprise Ar that is:



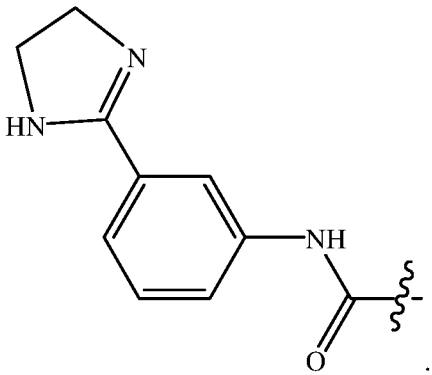
Still further, according to some embodiments, the compounds of Formula I used by the methods of the invention may comprise Ar that is:



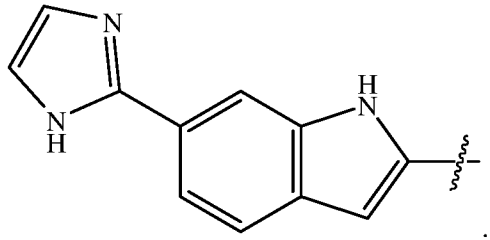
Still further, according to some embodiments, the compounds of Formula I used by the methods of the invention may comprise R that is:



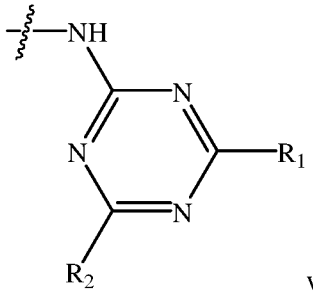
According to some further embodiments, the compounds of Formula I used by the methods of the invention may comprise R that is:



According to some embodiments, the compounds of Formula I used by the methods of the invention may comprise R that is:

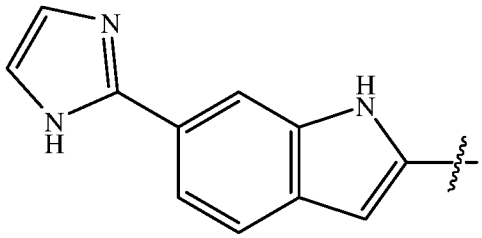


According to some embodiments, the compounds of Formula I used by the methods of the invention may comprise R that is:

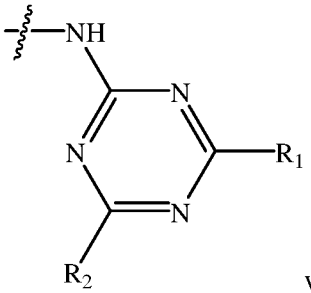


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine.

According to some embodiments, the compounds of **Formula I** used by the methods of the invention may comprise R that is:

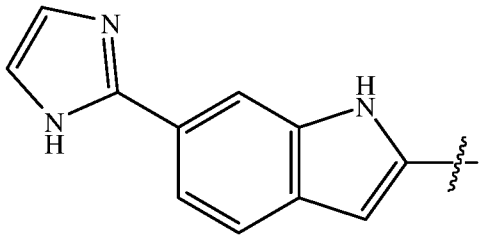


and R that is:

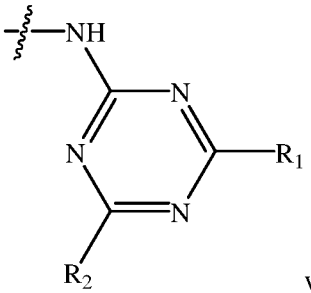


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine.

According to some embodiments, the compounds of Formula I used by the methods of the invention may comprise R that is:

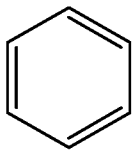


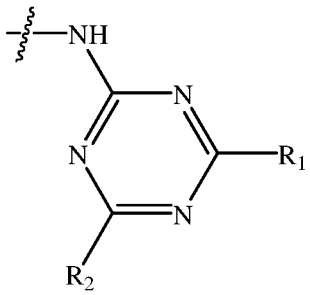
and R that is:



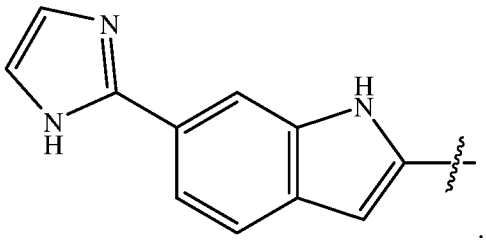
wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$.

Any combination of the above depicted one or more of said Ar and one or more of said R is within the scope of the presented disclosure.

For example, in some embodiments Ar is , at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



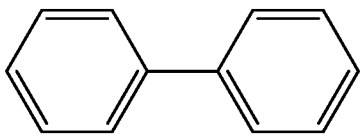
.

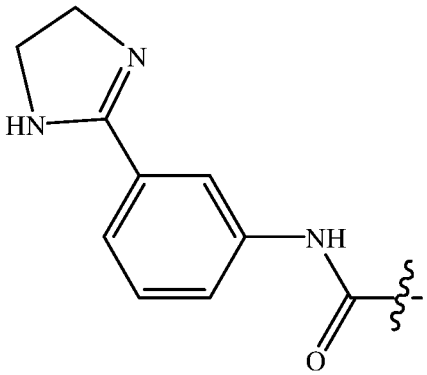
Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 2 and the two R groups may be oriented in para-position on the Ar group, relative to each other.

In some embodiments n is 2 and the two R groups may be oriented in meta-position on the Ar group, relative to each other.

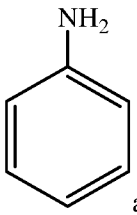
In some embodiments n is 2 and the two R groups may be oriented in ortho-position on the Ar group, relative to each other.

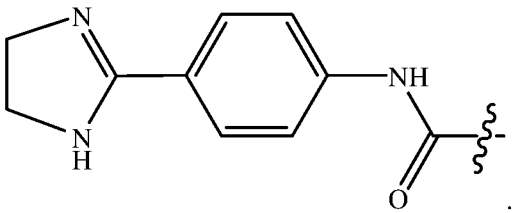
In some embodiments Ar is  and at least one of R is



Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 2 and the two R groups may be symmetrically oriented relative to each other on the Ar group.

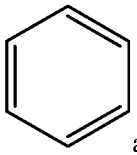
In some embodiments Ar is  and at least one of R is

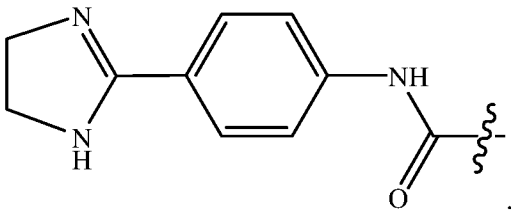


.

Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 2 and the two R groups may be para-oriented relative to each other on the Ar group.

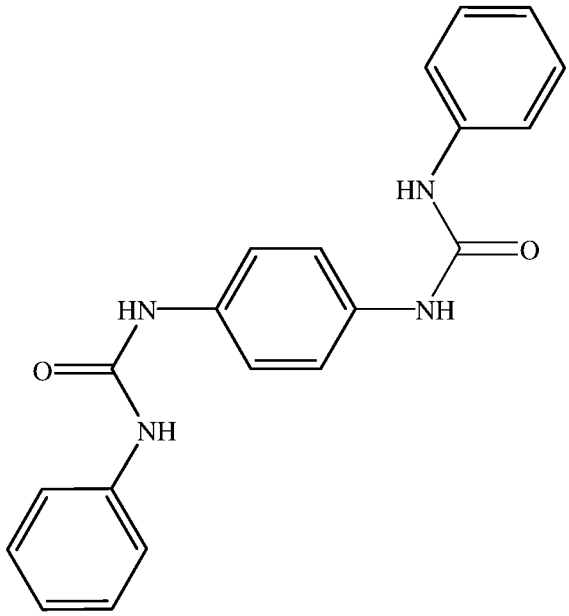
In some embodiments Ar is  and at least one of R is

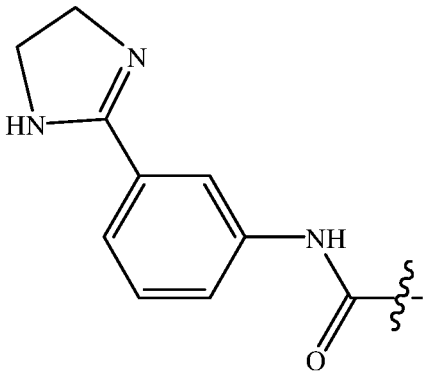


.

It should be noted that any one of said Ar and R may optionally be further substituted.

In some embodiments n is 3 and the three R groups may be meta-oriented relative to each other on the Ar group.

In some embodiments Ar is  and at least one of R is



Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 4 and the four R groups may be symmetrically oriented relative to each other on the Ar group.

As used herein the term "***aromatic moiety***" refers to a moiety that comprises at least one aromatic group. The at least one aromatic group may be a single aromatic ring or a group of multiple/poly aromatic rings (e.g., up to three rings). The multiple/poly aromatic rings may be fused together or linked covalently. The "***aromatic moiety***" may comprise one or more of said aromatic ring and/or group of multiple/poly aromatic rings. At times the multiple rings may be directly covalently bonded or via a linker linking between the aromatic rings. Non limiting example of such a linker is the group -NH-C=(O)-NH-. In some embodiments the aromatic moiety comprises two or more aromatic groups linked by one or more of said linker. The "***aromatic moiety***" may

comprise at least one aromatic group with at least one heteroatom. To this end the "***aromatic moiety***" is referred to herein as a "***heteroaromatic moiety***". The "***heteroaromatic moiety***" may comprise from one to five heteroatoms selected from N, O, and S. At times the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen atom(s) may optionally be quaternized. At times the heteroaromatic group may be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aromatic moieties include benzene, naphthalene, fluorene, anthracene, phenanthrene, phenalene, biphenyl, toluene, and aniline, while non-limiting examples of heteroaromatic groups include pyridyl, pyridazinyl, pyrazinyl, pyrimindinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalaziniyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzooxazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, pyrrolopyridyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like. Each possibility is within the scope of the present disclosure.

In some embodiments, each of Ar and R of the compounds disclosed herein, may optionally be further substituted (independent of each other) with one or more substituents. Suitable substituents include but are not limited to halogen (e.g., Cl, Br, F, I), -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} haloalkyl, straight or branched $-O-C_{1-5}$ haloalkyl, straight or branched $-S-C_{1-5}$ alkyl, straight or branched $-O-C_{1-5}$ alkyl, straight or branched C_{1-5} alkoxy (e.g., -OMe, -O-Ethyl, -O-Propyl, -O-Isopropyl), straight or branched C_{1-5} amine, straight or branched C_{1-5} amide, and CN. Each possibility is within the scope of the present disclosure.

As used herein the term "***imidazole derivative***" refers to a moiety that comprises a saturated or an unsaturated hetero five-membered ring containing two nitrogen atoms at positions 1 and 3. The term also encompasses a dihydroimidazole derivative. Non limiting examples of imidazole derivatives are 4,5-dihydro-1*H*-imidazole, 1*H*-imidazole, 2-methyl-1*H*-imidazole, benzimidazole, 2-methylbenzimidazole, 2-phenylimidazole, 4,5-diphenylimidazole, and 2,4,5-triphenylimidazole. Each possibility is within the scope of the present disclosure.

In some embodiments the imidazole derivative may optionally be further substituted e.g., as detailed herein above in connection with group R.

As used herein, the term "***triazine derivative***" refers to a moiety that comprises an unsaturated ring of three carbon and three nitrogen atoms. The following three triazine isomers are within the scope of the present disclosure: 1,2,3-triazine; 1,2,4-triazine; and 1,3,5-triazine (s-triazine).

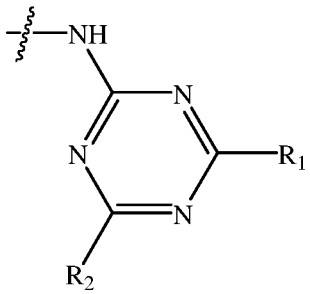
In some embodiments the triazine derivative is 1,3,5-triazine derivative.

In some embodiments the triazine derivative may optionally be further substituted e.g., as detailed herein above in connection with group R..

The term "***halogen***" or "***halo***" as used herein refers to Cl, Br, F, and I atoms.

In some embodiments the halogen is selected from the group consisting of Cl, Br, F, and I. In some embodiments said halogen is Cl. In some embodiments said halogen is Br. In some embodiments said halogen is F. In some embodiments said halogen is I. Each possibility is within the scope of the present disclosure.

In some embodiments in the compound of the present invention at least one of R is



wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine.

In some embodiments, R_1 is Cl. In some embodiments, R_1 is Br. In some embodiments, R_1 is F. t In some embodiments R_1 is I. In some embodiments R_2 is Cl. In some embodiments R_2 is Br. In some embodiments R_2 is F. In some embodiments R_2 is I. Each possibility is within the scope of the present disclosure.

In some embodiments R_1 is hydrogen. In some embodiments R_1 is -OH. In some embodiments R_1 is $-NH_2$. In some embodiments R_2 is hydrogen. In some embodiments R_2 is -OH. In some embodiments R_2 is $-NH_2$. Each possibility represents another aspect of the present disclosure.

In some embodiments R_1 and/or R_2 (independently of the other) are methyl. In some embodiment R_1 and/or R_2 (independently of the other) are ethyl. In some embodiments

R_1 and/or R_2 (independently of the other) are propyl. In some embodiments, R_1 and/or R_2 (independently of the other) are butyl. In some embodiments R_1 and/or R_2 (independently of the other) are pentyl. Each possibility represents another aspect of the present disclosure.

In some embodiments R_1 is methoxy. In some embodiments R_1 is ethoxy. In some embodiments R_1 is n-propoxy. In some embodiments R_1 is isopropoxy. In some embodiments R_1 is n-butoxyl. In some embodiments R_1 is t-butoxyl. In some embodiments R_1 is pentoxy. In some embodiments R_2 is methoxy. In some embodiments R_2 is ethoxy. In some embodiments R_2 is n-propoxy. In some embodiments R_2 is isopropoxy. In some embodiments R_2 is n-butoxy. In some embodiments R_2 is t-butoxyl. In some embodiments R_2 is pentoxy. Each possibility is within the scope of the present disclosure.

The term "***amine***" as used herein refers to the group -NR'R'', wherein R' and R'' may be independently selected from hydrogen, C_{1-5} alkyl or aryl. Other applicable substituents is withing the scope of the present disclosure. In some embodiment the amine group is $-NH_2$. In some embodiments the amine is a "***C_{1-5} alkylamine***" group.

The term "***alkyl***" as used herein refers to a saturated aliphatic hydrocarbon, including straight-chain also referred to as a linear-chain, and a branched-chain. In some embodiments the alkyl group has 1-5 carbons designated herein as C_{1-5}-alkyl. In some embodiments the alkyl group has 1-4 carbons designated here as C_{1-4}-alkyl. In some embodiments the alkyl group has 2-5 carbons designated herein as C_{2-5}-alkyl. In some embodiments the alkyl group has 2-4 carbons designated herein as C_{2-4}-alkyl. Each possibility is within the scope of the present disclosure. The alkyl group may be unsubstituted or substituted e.g., by one or more groups selected from the group consisting of hydroxyl, halogen, amino, thiol, phosphate. In some embodiments the alkyl is methyl. In some embodiments the alkyl is ethyl. In some embodiments the alkyl is propyl. In some embodiments the alkyl is butyl. In some the alkyl is pentyl.

The term "***C_{1-5} alkoxy***" as used herein refers to C_{1-5} alkyl (hydrocarbon chain) group singularly bonded to oxygen. Non limiting examples are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and the like. In some embodiments the alkoxy group is methoxy. The term "***C_1 to C_5 substituted alkoxy***" means the alkyl portion of the alkoxy can be substituted in the same manner as in relation to C_{1-5} substituted alkyl. Similarly,

the term "***C_{1-5} phenylalkoxy***" as used herein means "***C_{1-5} alkoxy***" bonded to a phenyl radical. Each possibility is within the scope of the present disclosure.

In some embodiments, in the compounds of the present disclosure n is an integer from 1 to 10. In some embodiments n is an integer from 1 to 2. In some embodiments n is an integer from 1 to 3. In some embodiments n is an integer from 1 to 4. In some embodiments n is an integer from 1 to 5. In some embodiments n is an integer from 1 to 6. In some embodiments n is an integer from 1 to 7. In some embodiments n is an integer from 1 to 8. In some embodiments n is an integer from 1 to 9. In some embodiments n is an integer from 2 to 3. In some embodiments n is an integer from 2 to 4. In some embodiments n is an integer from 2 to 5. In some embodiments n is 1. In some embodiments n is 2. In some embodiments n is 3. In some embodiments n is 4. In some embodiments n is 5. In some embodiments n is 6. In some embodiments n is 7. In some embodiments n is 8. In some embodiments n is 9. In some embodiments n is 10. In some embodiments n is 2, 3, or 4. In some embodiments n is 2 or 3. In some embodiments n is 3 or 4. Each possibility is within the scope of the present disclosure.

In some embodiments, wherein n>1 e.g., being an integer from 2 to 9, any one of the R may be the same or different, and the orientation thereof on the Ar group may vary. For example, in some embodiments the orientation may be any one of para-, meta- and ortho- orientation. At times the orientation may be symmetric e.g., with respect to the Ar moiety. At times the orientation may be non-symmetric e.g., with respect to the Ar moiety.

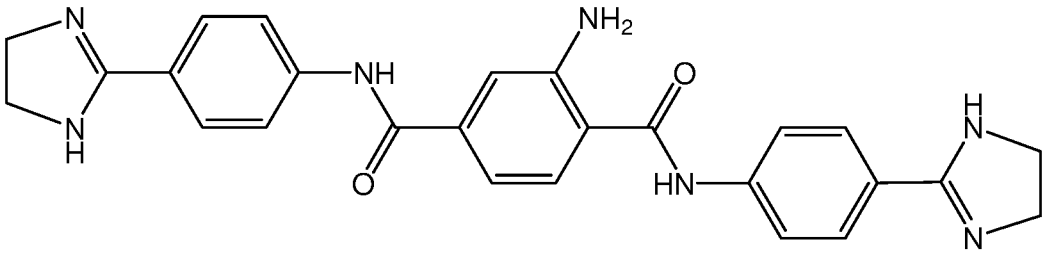
As used herein the term "***isomer***" refers to molecules with identical molecular formulae i.e., that is, same number of atoms of each element but distinct arrangements of atoms in space. The present disclosure encompasses isomers of the compounds of the invention. In some embodiments the isomers are constitutional (structural) isomers. In some embodiments the isomers are stereoisomer (spatial isomers). Isomers such as cis/trans, conformers, rotamers, tautomers, diastereomers and enantiomers are within the scope of the present disclosure.

It should be understood that the small molecule compounds as disclosed herein above and below and any derivatives thereof, are applicable for each and every aspect of the present disclosure.

In some embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of any one of **Formula III**, **IV**, **V**, **VI** and **VII**, any salt thereof and any combinations thereof.

In yet some specific embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula III**.

More specifically, the compound of **Formula III** is:

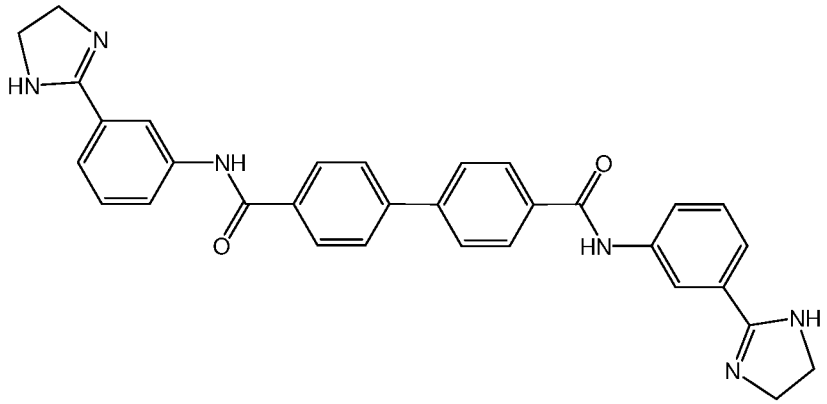


Formula III

a salt thereof, or any conjugates thereof.

In some embodiments, this compound may be referred to herein, as: NC1=C(C=CC(=C1)C(=O)NC2=CC=C(C=C2)C3=NCCN3)C(=O)NC4=CC=C(C=C4)C5=NCCN5 i.e., the simplified molecular-input line-entry system (SMILES). In yet some further embodiments, the compound of **Formula III**, may be referred as 2-amino-N^1, N^4-bis(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl) terephthalamide (ACD/Name 4.0); NSC # 50469; CAS # 73-57-4; Formula: $C_{26}H_{25}N_7O_2$; Mw: 467.5292 gr/mol. In yet some further embodiments, a salt form of the compound of **Formula III**, may be referred to herein as Tetephthalanide, 2-amino4', 4"-di-2-imidazolin-2-yl, dihydrochloride or 1,4-Benzenedicarboxamide, 2-amino-N, {N'-bis[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-,} dihydrochloride. As used herein, this compound of **Formula III**, is also designated by the present disclosure as compound #2.

In yet some further embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula IV**. More specifically, the compound of **Formula IV** is:

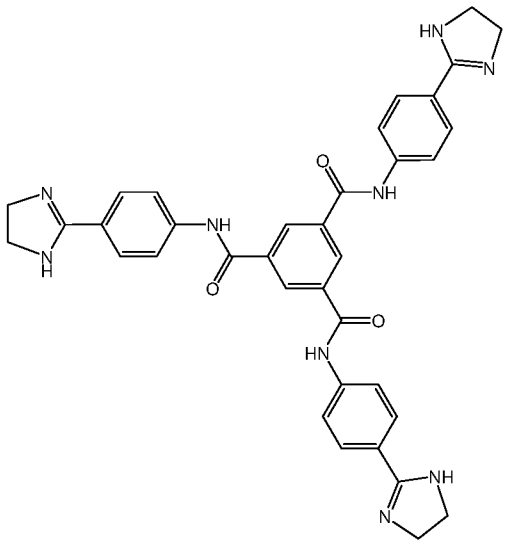


Formula IV

a salt thereof, or any conjugates thereof.

In some embodiments, this compound may be referred to as O=C(NC1=CC(=CC=C1)C2=NCCN2)C3=CC=C(C=C3)C4=CC=C(C=C4)C(=O)NC5=CC(=CC=C5)C6=NCCN6 (SMILES), or alternatively, this compound may be referred as N^4,$N^{4'}$-bis(3-(4,5-dihydro-1H-imidazol-2-y-l)phenyl)[1,1'-biphenyl]-4,4'-dicarboxamide (ACD/Name 4.0) NSC # 50460; CAS # 5352-53-4; Formula: $C_{32}H_{28}N_6O_2$; Mw: 528.6122 gr/mol. As used herein, this compound of **Formula IV**, is also designated by the present disclosure as compound #1.

In some further embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula V**. More specifically, the compound of Formula V is:

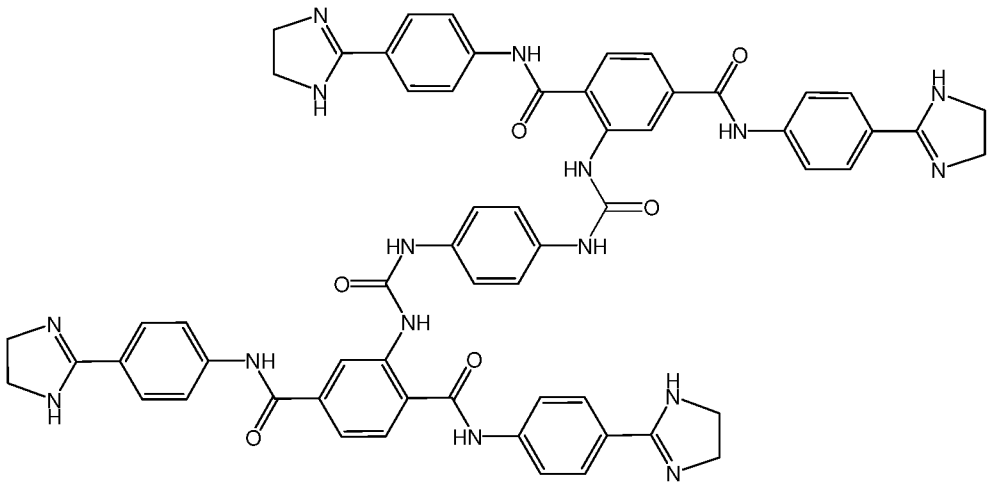


Formula V

a salt thereof, any conjugates thereof.

In some embodiments, this compound may be referred to as O=C(NC1=CC=C(C=C1)C2=NCCN2)C3=CC(=CC(=C3)C(=O)NC4=CC=C(C=C4)C5=NCCN5)C(=O)NC6=CC=C(C=C6)C7=NCCN7 (SMILES). Alternatively, the compound of Formula V may be referred to herein as N^1,N^3,N^5-tris(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,3,5-benzenetricarboxamide (ACD/Name 4.0); NSC # 57161; CAS # 5373-31-9; Formula: $C_{36}H_{33}N_9O_3$; Mw: 639.7152 gr/mol. As used herein, this compound of **Formula V**, is also designated by the present disclosure as compound #3.

Still further, in some embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula VI**. More specifically, the compound of **Formula VI** is:

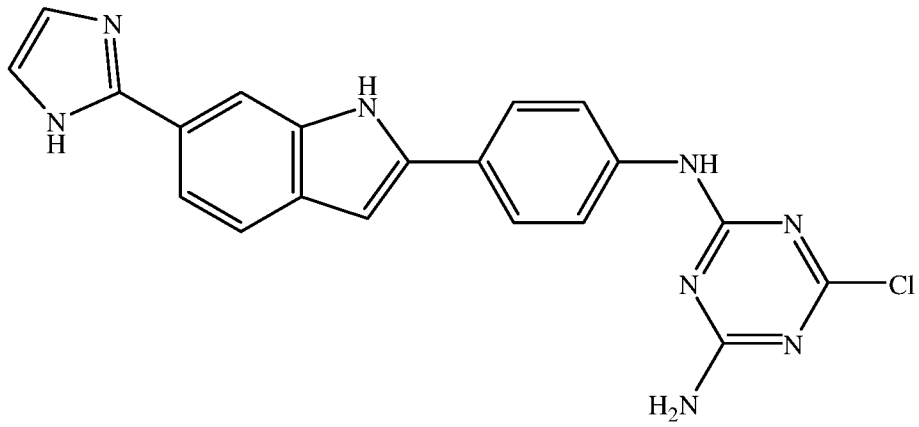


Formula VI

a salt thereof, any conjugates thereof. In some embodiments, this compound may be referred to as O=C(NC1=CC=C(NC(=O)NC2=C(C=CC(=C2)C(=O)NC3=CC=C(C=C3)C4=NCCN4)C(=O)NC5=CC=C(C=C5)C6=NCCN6)C=C1)NC7=C(C=CC(=C7)C(=O)NC8=CC=C(C=C8)C9=NCCN9)C(=O)NC%10=CC=C(C=C%10)C%11=NCCN%11 (SMILES). Alternatively, this compound may be referred to herein as 2-(((4-(((2,5-bis((4-(4,5-dihydro-1H-imidazol-2-yl)anilino)carbonyl)anilino)carbonyl)amino)anilino)carbonyl)amino)-N^1,N^4-bis(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)terephthalamide(ACD/Name 4.0). Urea, {N,N-[1,4-

phenylenebis[N'-[2,5-bis[[4-(4,5-dihydro-}1H-imidazol-2-yl) phenyl\]amino\]carbonyl\]phenyl\]; NSC # 63676; CAS # 5548-83-4; Formula: $C_{60}H_{54}N_{16}O_6$; Mw: 1095.1902 gr/mol. As used herein, this compound of **Formula VI**, is also designated by the present disclosure as compound #4.

Yet in some further embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula VII**. More specifically, the compound of **Formula VII** is:



Formula VII

a salt thereof, any conjugates thereof.

In some embodiments, this compound may be referred to as NC1=NC(=NC(=N1)Cl)NC2=CC=C(C=C2)C3=CC4=C([NH]3)C=C(C=C4)C5=NC=C [NH]5 (SMILES). Still further, the compound of **Formula VII**, may be referred to herein as 6-chloro-N^2-(4-(6-(1H-imidazol-2-yl)-1H-indol-2-yl)phenyl)-1,3,5-triazine-2,4-diamine (ACD/Name 4.0); NSC # 364277; Formula: $C_{20}H_{15}ClN_8$; Mw: 402.8451 gr/mol. As used herein, this compound of **Formula VII**, is also designated by the present disclosure as compound #6.

As indicated above, the present disclosure provides methods using the disclosed small molecule compounds derived from the compounds of **Formula I** and/or **II**, for inhibiting at least one metastatic property of a cell. As used herein, **metastasis**, is the spread of cancer cells to new areas of the body (often by way of the lymph system or bloodstream). A metastatic cancer, or metastatic tumor, is one which has spread from the primary site of origin (where it started) into different area(s) of the body (secondary

sites). Tumors formed from cells that have spread are called secondary tumors (metastases). The cancer may have spread to areas near the primary site (regional metastasis), or to **distal sites** that are parts of the body further away (distant metastasis). Metastasis is a multi-step process. The term "**metastatic cascade" is related to such multi-step process.** In an initial step of the metastatic cascade (i) cancer cells locally infiltrate adjacent tissue by invading through basement membrane and migrating through the tumor stroma; in the next step (ii), cancer cells transmigrate through the blood or lymph vessels' endothelial layer, known as intravasation into vasculature. In the following step (iii), cancer cells must survive the challenges of the blood stream including physical constraints and the immune system circulation, while evading clearance by the immune system, and attaching to blood vessels around secondary sites. Following that (iv), cancer cells extravasate through the endothelial barrier. In the final step (v), cancer cells proliferate to colonialize the metastatic target. **The term "Metastatic property of a cell"** in the context of the present disclosure, relates to at least one of several cellular characteristics of the metastatic cell, essentially involved in at least one of several steps of the metastatic cascade. Such cellular characteristics include, but are not limited to, the ability of metastatic cells to: invade (Cell invasion), migrate (Cell migration), change location by consuming energy (Cell motility), adhere to other cells and extracellular molecules (Cell adhesion), and colonialize at secondary site (Cell proliferation).

Thus, in some embodiments, the metastatic property reduced by the method of the present disclosure, may be at least one of cell invasiveness, cell motility, cell migration and cell adhesion. More specifically, in some embodiments, the small molecule compounds of **Formula I** and/or **II** used in the methods disclosed herein, inhibit and/or reduce migration of cancer cells. The term **"Cell migration",** relates to a central process in the development and maintenance of multicellular organisms. Tissue formation during embryonic development, wound healing and immune responses require the orchestrated movement of cells in particular directions to specific locations. Cells often migrate in response to specific external signals, including chemical signals and mechanical signals. Cells achieve active movement by several different mechanisms and generally involves drastic changes in cell shape which are driven by the cytoskeleton. There are two models for cell migration: the cytoskeletal model and the membrane flow model. It seems that both underlying processes contribute to cell

extension. More specifically, the cytoskeletal model, rapid actin polymerization at the cell's front edge leads to the formation of actin filaments that "push" the leading edge forward. This is the main motile force for advancing the cell's front edge. According to the membrane flow model, extension of the leading edge occurs primarily by addition of membrane at the front of the cell. The actin filaments that form at the front might stabilize the added membrane so that a structured extension, or lamella, is formed rather than a bubble-like structure (or bleb) at its front. As cell migration enhances the metastatic potential of tumor cell/s, in some embodiments, the compounds of **Formula I**, and/or **II** of the invention as well as methods using these small molecule compounds, inhibit cell migration and motility, as also shown by the Examples.

In some embodiments, the small molecule modulators of the invention inhibit and/or reduce motility of cancer cells. More specifically, **"Cell motility"**, refers to the spontaneous movement of a cell from one location to another by consumption of energy. The term encompasses several types of motion, including swimming (or flagellar motility), crawling (or amoeboid movement), gliding and swarming. The small molecule compounds of any one of **Formulas I** to **VII**, provided by the present disclosure and used by of the methods provided herein may in some embodiments, modulate, and specifically in some embodiments inhibit any of the cell motility type discussed herein.

Still further, in some embodiments, the small molecule compounds of any one of **Formulas I** to **VII**, provided by the present disclosure may modulate, and specifically decrease cell invasion. **The term "Cell invasion"**, or **"cell invasiveness"**, relates to cell migration and defines the ability of cells to become motile and to navigate through the extracellular matrix within a tissue or to infiltrate neighboring tissues. Cancer cells that become invasive may disseminate to secondary sites and form metastases.

In yet some further embodiments, the small molecule compounds and methods provided by the invention may modulate cell adhesion. The term **"Cell adhesion"**, as used herein, relates to a process by which cells interact and attach to a surface, substrate or another cell, mediated by interactions between molecules of the cell surface. Cell adhesion occurs from the action of transmembrane glycoproteins, called cell adhesion molecules. Examples of these proteins include selectins, integrins, syndecans, and cadherins. Cellular adhesion is essential in maintaining multicellular structure. Thus, in some embodiments, the expression and/or activity of molecules that modulate cell

adhesion may be affected by the disclosed compounds. Cancer metastasis tumors that spread through the circulatory system use mechanisms of cell adhesion to establish new tumors in the body. Yet, the Inventors have previously shown that knockdown by genetic means of the SKAI1BC lncRNA has led to increased wound healing and elevated adhesion to fibronectin (Aram et al., 2017). Therefore, the small molecule compounds of any one of **Formulas I** to **VII**, provided by the present disclosure may enhance cell adhesion, thereby reducing the metastatic potential of tumor cells.

More specifically, the terms **"inhibition", "moderation", "reduction" or "attenuation"** as referred to herein, relate to the retardation, restraining and/or reduction of at least one of cell invasion/metastasis, cell migration, cell motility, cell adhesion, in cell/s, tissue/s and/or subject/s, by any of the compounds of the present disclosure, by any one of about 1% to 99.9%, specifically, about 1% to about 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, about 45% to 50%, about 50% to 55%, about 55% to 60%, about 60% to 65%, about 65% to 70%, about 75% to 80%, about 80% to 85% about 85% to 90%, about 90% to 95%, about 95% to 99%, or about 99% to 99.9% or even 100%, as compared with cell/s, tissue/s and/or subject/s not treated with any one of the compounds of Formulas I-VII.

With regards to the above, it is to be understood that, where provided, percentage values such as, for example, 10%, 50%, 100%, 120%, 500%, etc., are interchangeable with "fold change" values, i.e., 0.1, 0.5, 1.2, 5, etc., respectively. The term **"inhibition"** and all variations of this term (**"moderation", "reduction" or "attenuation"**) is intended to encompass the restriction or prohibition of the progress and exacerbation of pathologic symptoms or a pathologic process progress, said pathologic process symptoms or process are associated with.

The disclosed methods involve the step of contacting the cell/s with an inhibitory effective amount of any of the small molecule compound of any one of **Formulas I** to **VII**, provided by the present disclosure, or with a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof or any vehicle, matrix, nano- or micro-particle, or composition comprising the same.

The term **"contacting"** means to bring, put, incubate or mix together. As such, a first item is contacted with a second item when the two items are brought or put together, e.g., by touching them to each other or combining them. In the context of the present

disclosure, the term "contacting" includes all measures or steps, which allow interaction between the small molecule compounds of any one of **Formulas I** to **VII**, provided by the present disclosure, and the metastatic cells to be modulated. The terms **"effective amount"** or "therapeutically effective amount" or "sufficient amount" used by the methods of the invention, mean an amount necessary to achieve a selected result.

In some embodiments, the method of the present disclosure reduces the at least one metastatic property of at least one cell that may be a mammalian malignant cancer cell.

The terms **"Malignancy" or "cancer"** are used equivalently to describe diseases in which abnormal cells divide without control and can invade nearby tissues and may be capable of spreading to distant tissues. In contrast with a non-cancerous benign disease. There are several main types of malignancy. **Carcinoma** is a malignancy that begins in the skin or in tissues that line or cover internal organs. **Sarcoma** is a malignancy that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. **Hematological malignancies** include **"non-solid"** or **"liquid"** tumors that affect the blood, bone marrow and lymphatic system: **Leukemia** is a malignancy that begins in blood-forming tissue, such as the bone marrow, and causes too many abnormal blood cells to be made. **Lymphoma and multiple myeloma** are malignancies that begin in the cells of the immune system. If the tissue is a part of the lymphatic or immune systems, malignant cells may include non-solid tumors ("liquid") of circulating cells. Malignancies of other tissues or organs may produce solid tumors. In general, the methods of the present invention may be applicable for treatment of non-solid ("liquid") and solid tumors. Accordingly, a "**Malignant cell**" is an abnormal cell that divide without control in-vitro and/or in-vivo and can invade nearby tissues and may be capable of spreading to distant tissues if present in-vivo.

The term **"mammalian"** refers to any member of the group of vertebrate animals in which the young are nourished with milk from special mammary glands of the mother. Some examples of mammals include livestock, equine, canine, rodents and feline subjects, primates and most specifically humans. Accordingly, the term **"mammalian cell"** is a cell of any mammalian origin and **the term "mammalian malignant cancer cell"** describes any abnormal cell, of mammalian origin, that divides without control and can invade nearby tissues and may be capable of spreading to distant tissues.

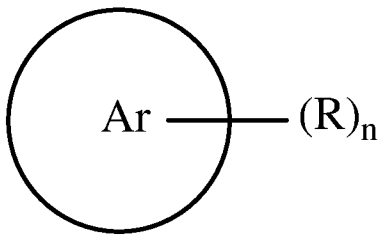
In some embodiments, the methods of the present disclosure lead to reduction in the at least one metastatic property of at least one mammalian malignant cancer cell originated

from at least one of breast tissue, bladder tissue, kidney tissue, hepatic tissue, pancreatic tissue, colorectal tissue, gastric tissue, lung tissue, skin tissue, ovarian tissue, prostate tissue, thyroid tissue, cervical tissue, endometrium tissue, bone tissue, laryngeal tissue and hematopoietic tissue (Lymphoid and Myeloid origin).

Yet, in some further embodiments, the method of the present disclosure is used to reduce the at least one metastatic property of at least one mammalian malignant cancer cell in a subject suffering from a malignant metastatic disease.

In some embodiments, the malignant proliferative disorder may be at least one primary and/or secondary malignancy of at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, and specifically, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer, hematopoietic malignancies (non-solid lymphoma, leukemia, or multiple myeloma).

More specifically, in some embodiments, the method comprises the step of administering to the subject a therapeutically effective amount of the compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof. more specifically, in some embodiments, wherein said **Formula I** is:



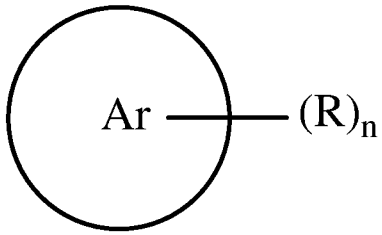
Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

It should be understood that the methods disclosed herein may be applicable for subjects suffering from any malignant metastatic disorder, specifically, any of the malignancies disclosed herein. In yet some further embodiments, the mammalian malignant cancer

cell manipulated by the methods of the present disclosure, expresses at least one antisense long non-coding RNA of the metastasis suppressor gene KAI1/cluster of differentiation 82 (CD82) (KAI1 as-lncRNA also named SKAI1BC lncRNA). In such case, the compounds of **Formulas II, III**, **IV**, **V**, and **VI**, as defined above may be used.

In another aspect, the present invention relates to an inhibitory effective amount of at least one small molecule compound for use in a method that results in the inhibition and/or reduction of at least one metastatic property of a cell. In some embodiments, the compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof. More specifically, **Formula I** is:

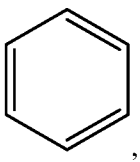


Formula I

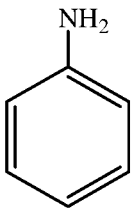
wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In some embodiments, Ar of the compound for use in the present disclosure, is selected from the group consisting of:

a)

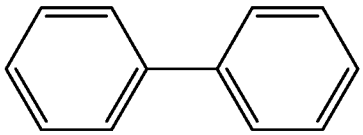

,

b)



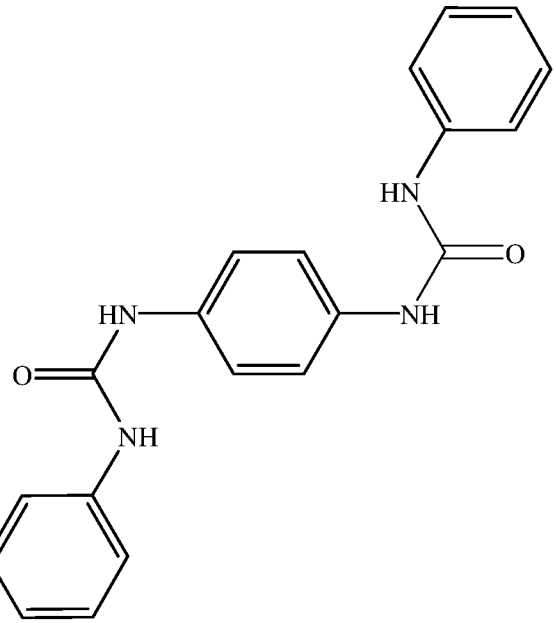
,

c)



, and

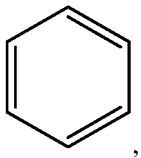
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)



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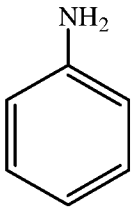
b)



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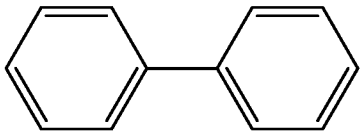
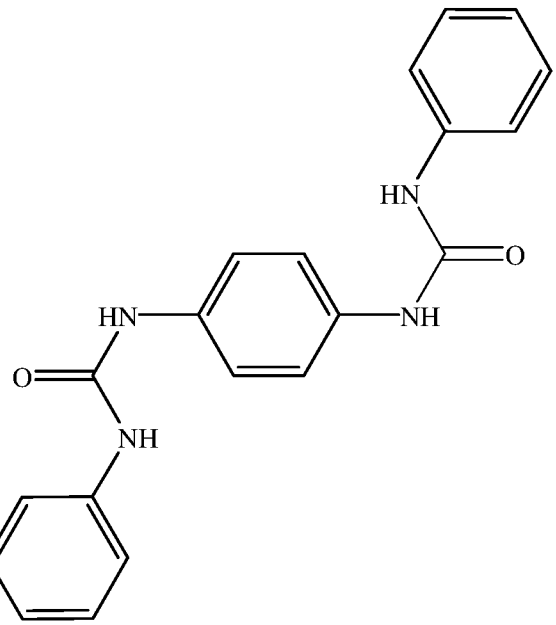
c)



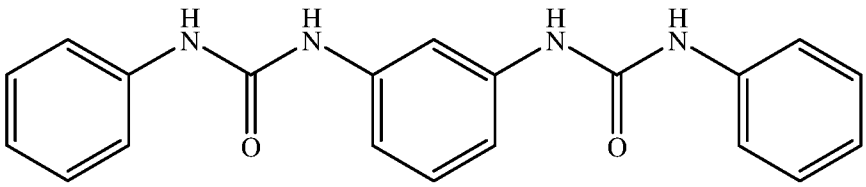
,

d)



, and

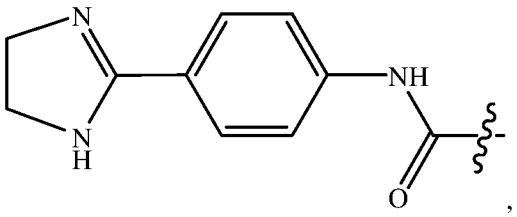
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

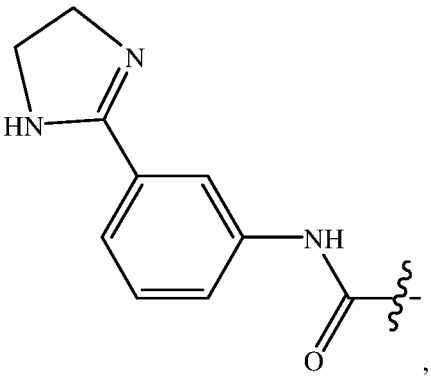
In yet some further embodiments, the R of the at least one small molecule compound of **Formula I** for use in the methods disclosed herein, may be selected from the group consisting of:

a)



,

b)



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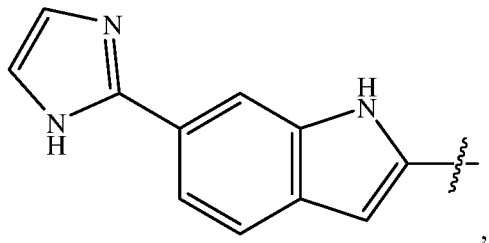
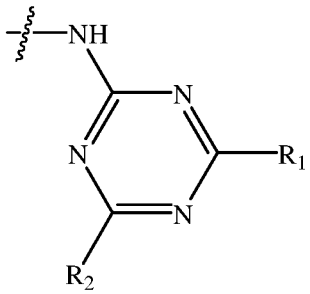
c)



, and

d)



wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

and wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

In some embodiments at least one of R is

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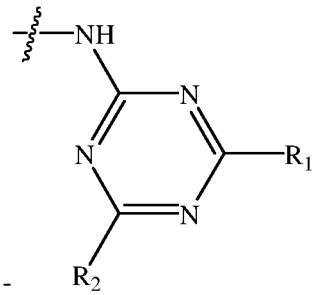
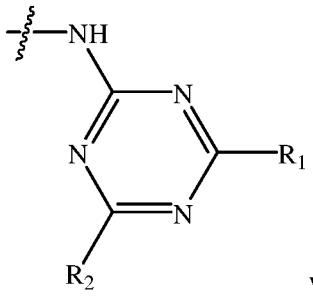


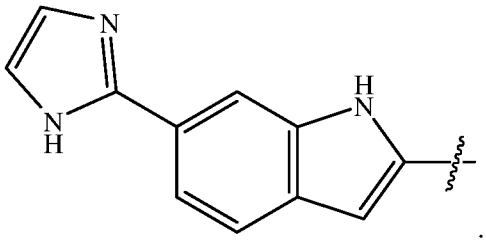
wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$.

In some specific embodiments of the method of the present disclosure, at least one of the R is an imidazole derivative and a triazine derivative.

In some embodiments at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



.

In some specific embodiments, the at least one of the R for use in the method of the present disclosure, is an imidazole derivative.

In some specific embodiments of the method of the present disclosure, the at least one of the R is a dihydroimidazole derivative.

In some specific embodiments of the method of the present disclosure, at least one of the R is a dihydroimidazole derivative.

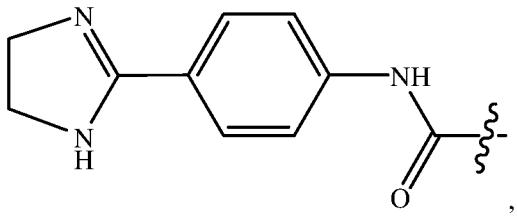
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative which may be the same or different.

In some further specific embodiments, the R of the compound for use in the methods of the present disclosure, may be repeated n times. In some embodiments, n may be 2, 3, or 4.

In some specific embodiments of the method of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

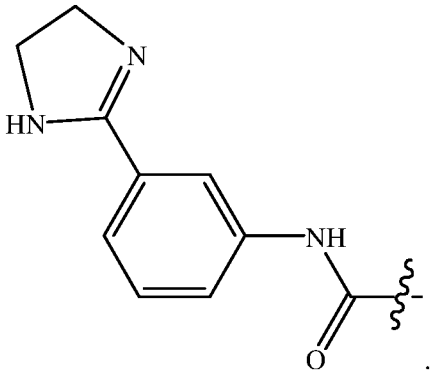
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



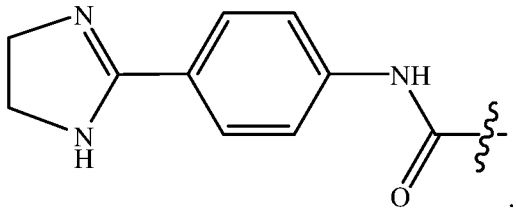
, or

b)



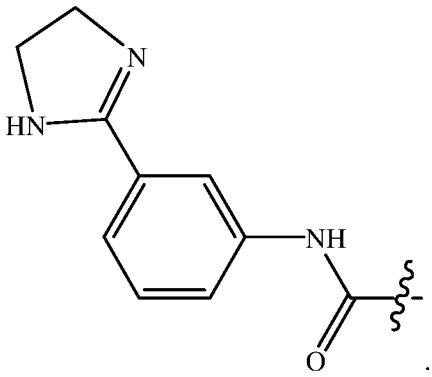
.

In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative

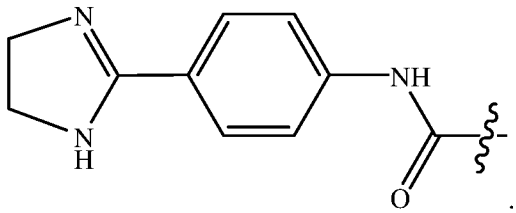


.

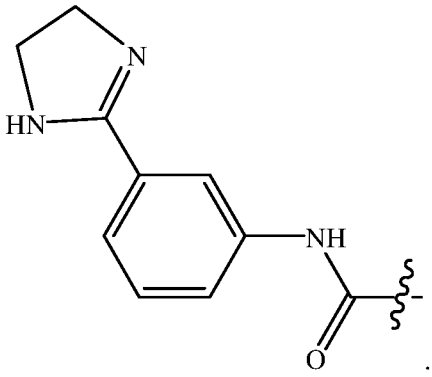
In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



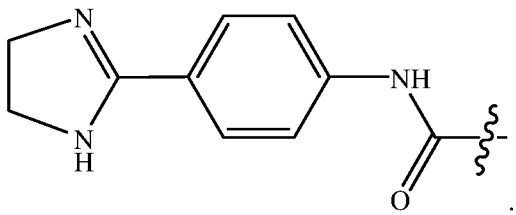
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



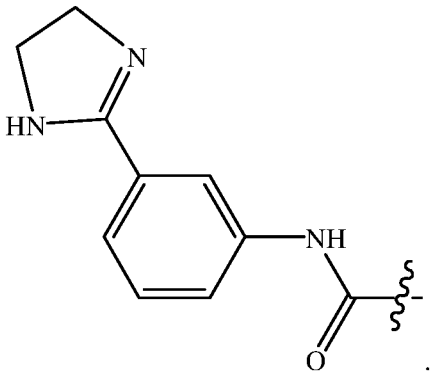
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative

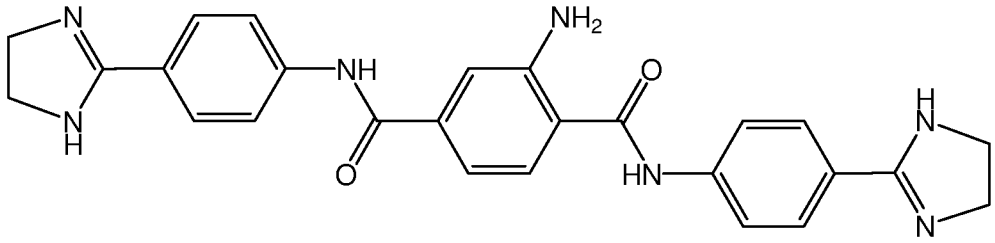


In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



In some embodiments, of the inhibitory effective amount of at least one small molecule compound for use in accordance with the present disclosure, the compound may be at least one of the compounds of **Formulas III**, **IV**, **V**, **VI** and/or **VII**, or any combinations thereof.

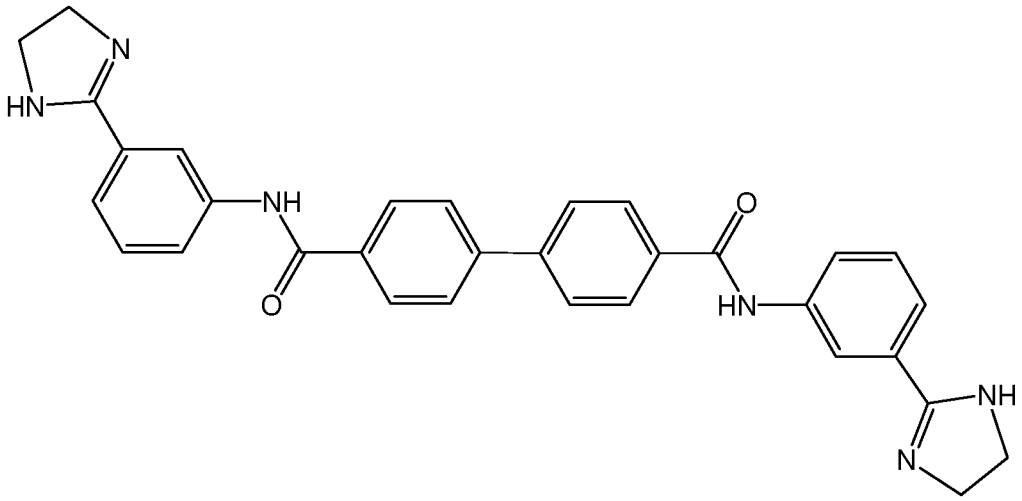
More specifically, in some embodiments, the compound for use may be the compound of **Formula III**, being:



Formula III

a salt thereof, or any conjugates thereof. In some embodiments, the compound of **Formula III**, is also designated by the present disclosure as compound #2.

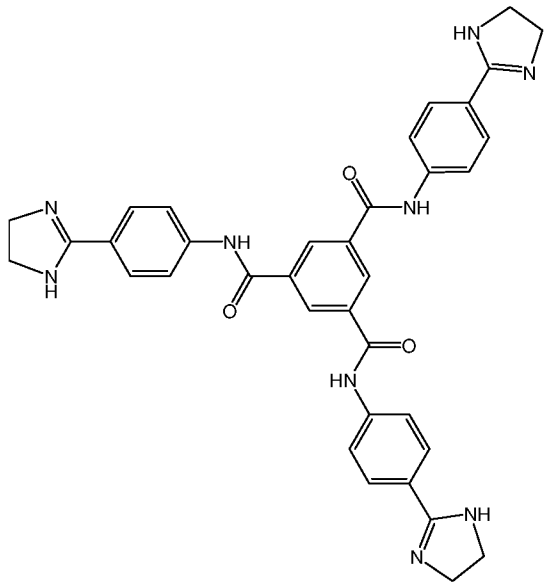
In yet some further embodiments, the compound for use in accordance with the present disclosure may be the compound of **Formula IV**, being:



Formula IV

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula IV**, is also designated by the present disclosure as compound #1.

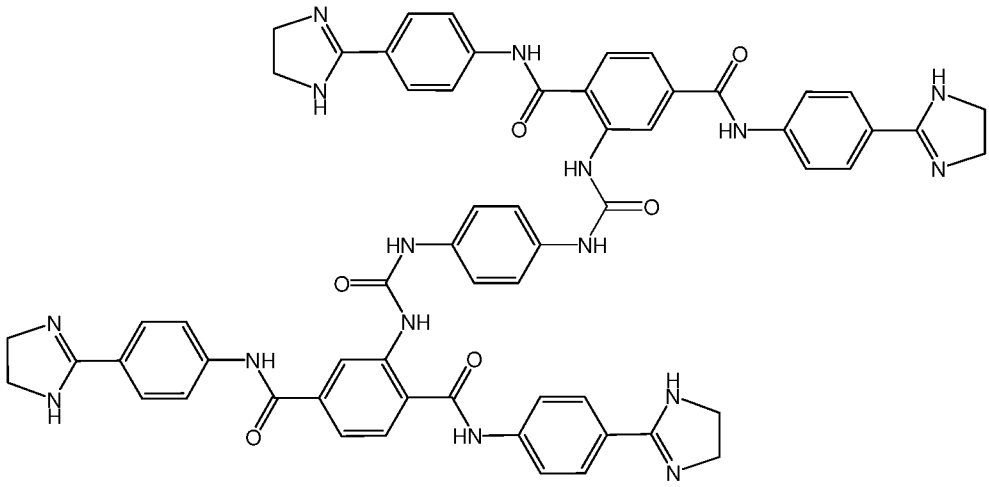
Still further, in some embodiments, the compound for use in accordance with the present disclosure may be the compound of **Formula V**:



Formula V

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula V**, is also designated by the preset disclosure as compound #3.

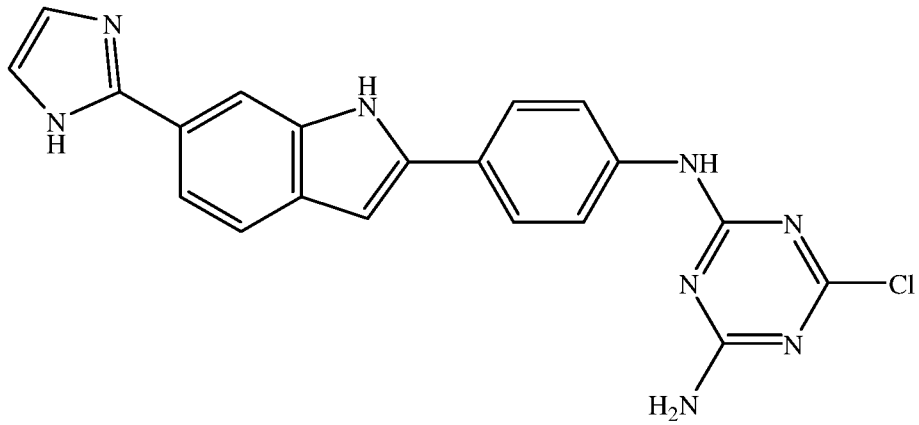
In some further embodiments, the compound for use in accordance with the present disclosure may be the compound of **Formula VI**:



Formula VI

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VI**, is also designated by the present disclosure as compound #4.

In some further embodiments, the compound for use in accordance with the present disclosure may be the compound of **Formula VII**:

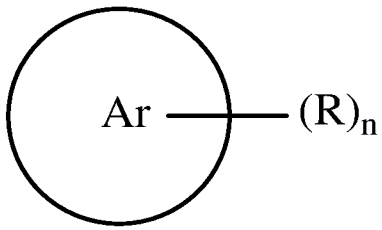


Formula VII

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VII**, is also designated by the present disclosure as compound #6.

In some embodiments, the at least one metastatic property inhibited and/or reduced by the inhibitory effective amount of the at least one small molecule compound used by the present disclosure, may be at least one of cell invasiveness, cell motility, cell migration and cell adhesion.

In yet another aspect thereof, the present invention provides methods of inhibiting and/or reducing, and/or delaying, and/or preventing a metastatic process, or at least one step or stage of a metastatic process, in a subject in need thereof. More specifically, the method comprising the step of administering to the subject a therapeutically effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof, or any composition thereof. In some embodiments, **Formula I** is

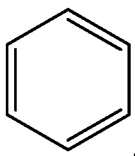


Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

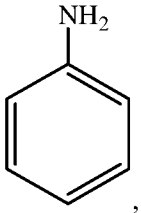
In some embodiments of the method disclosed herein, the Ar of the compound used is selected from the group consisting of:

a)



,

b)



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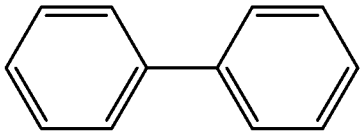
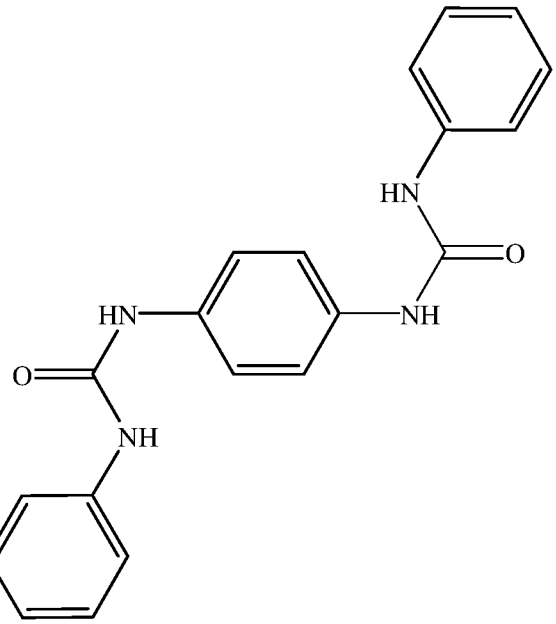
c)



, and

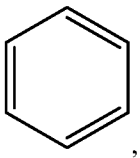
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted

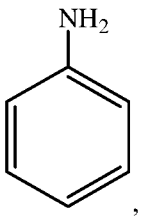
In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)



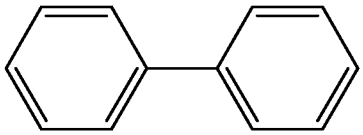
,

b)



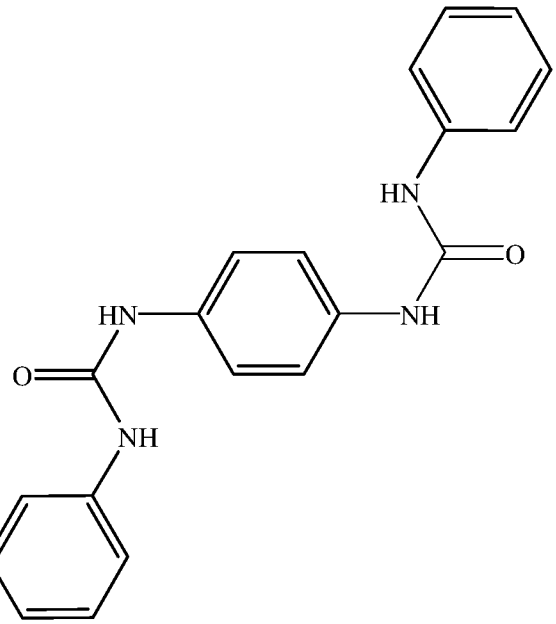
,

c)



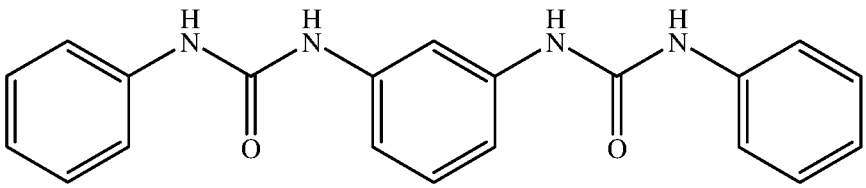
,

d)



, and

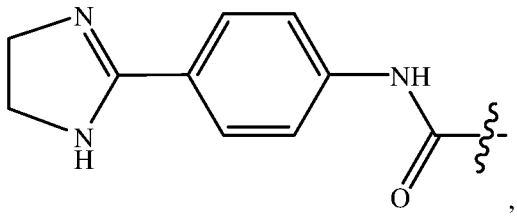
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some further embodiments of the method disclosed herein, the R of the compound used is selected from the group consisting of:

a)



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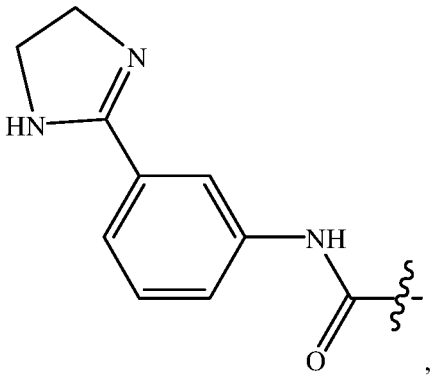
b)



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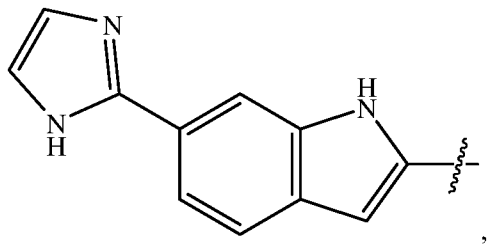
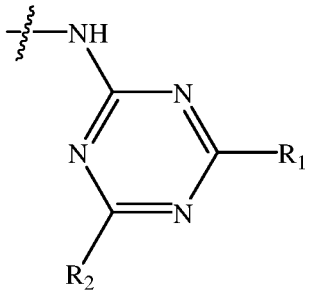
c)



, and

d)

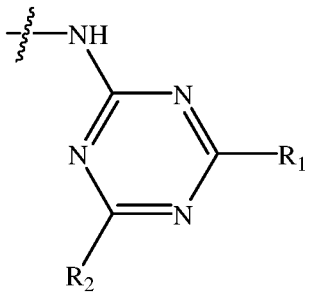


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

and wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

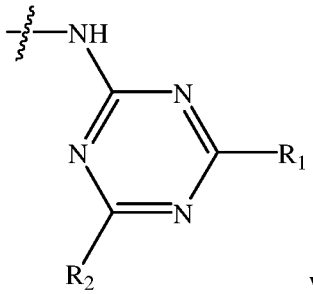
In some embodiments at least one of R is



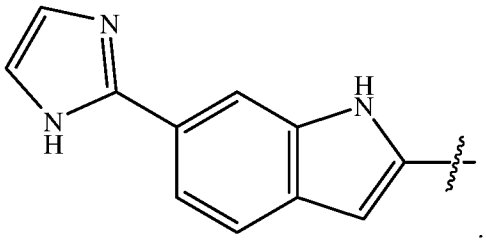
wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$.

In some specific embodiments of the method of the present disclosure, at least one of the R is an imidazole derivative and a triazine derivative.

In some embodiments at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



In some specific embodiments of the methods disclosed herein, the at least one of said R is an imidazole derivative.

In some specific embodiments of the method of the present disclosure, the at least one of the R is a dihydroimidazole derivative.

In some specific embodiments of the method of the present disclosure, at least one of the R is a dihydroimidazole derivative.

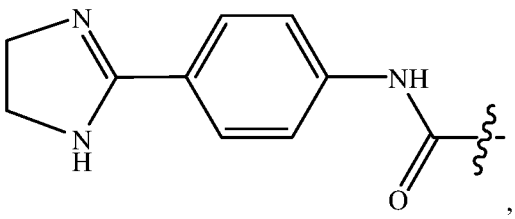
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative which may be the same or different.

In some more embodiments of the method disclosed herein, R of the compound used by the methods may be repeated n times, wherein n is 2, 3, or 4.

In some specific embodiments of the method of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

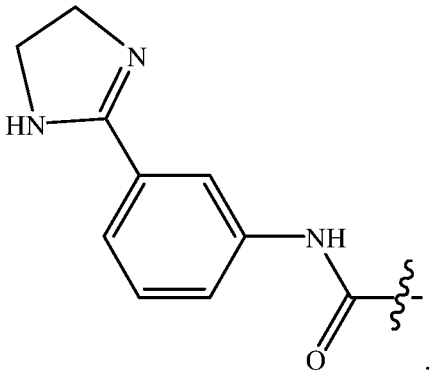
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



, or

b)



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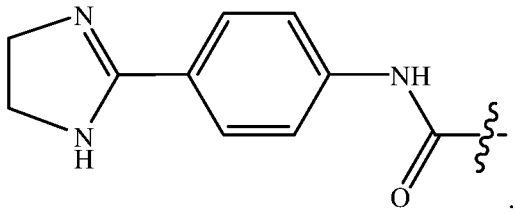
In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



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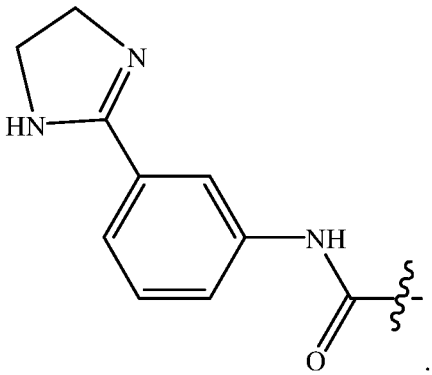
In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



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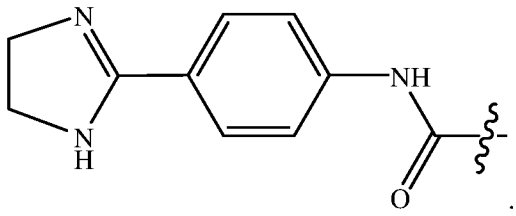
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



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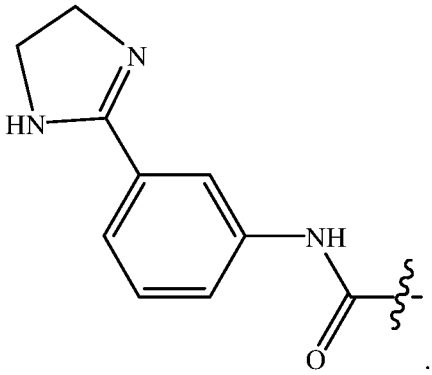
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



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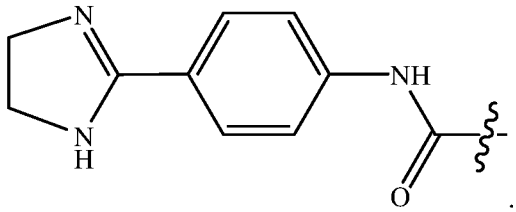
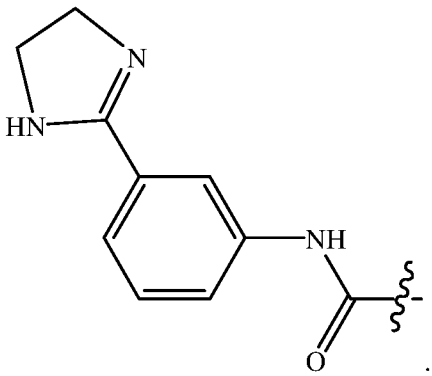
In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



.

In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



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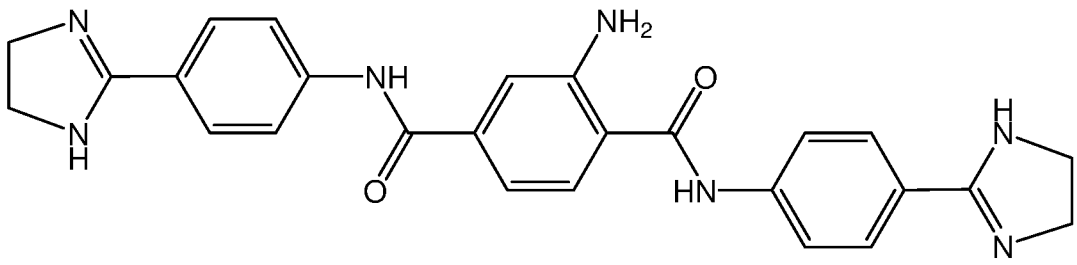
In yet some more embodiments of the method disclosed herein, the compound used may be at least one of the compounds of **Formulas III**, **IV**, **V**, **VI**, and/or **VII**.

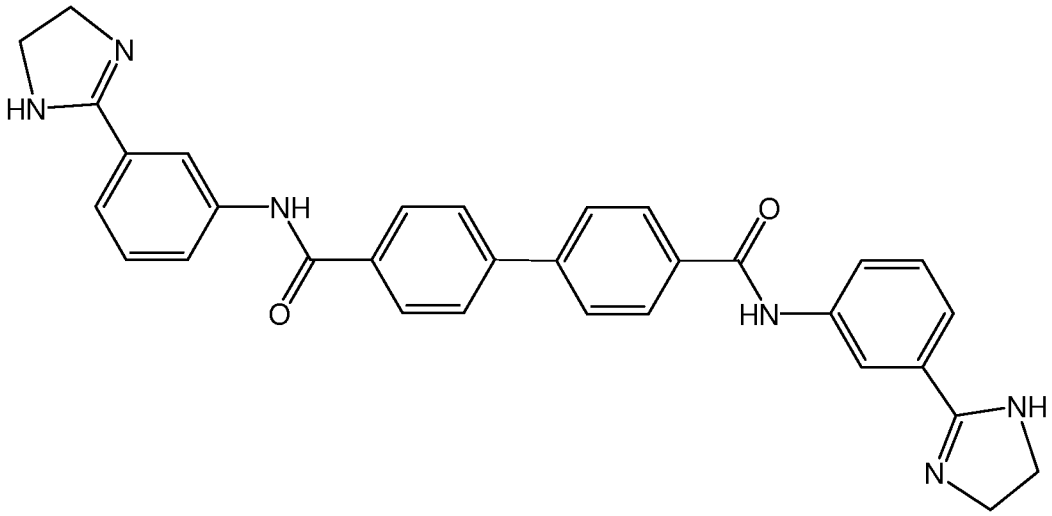
In some specific embodiments, the compound used in the methods of the present disclosure may be the compound of **Formula III**:



Formula III

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula III**, is also designated herein as compound #2.

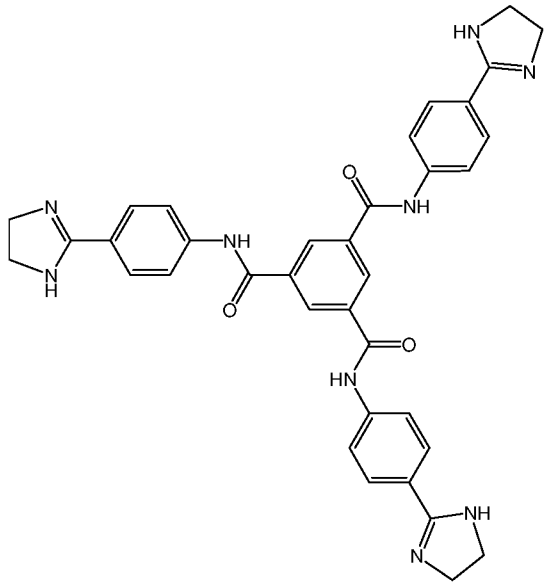
In some further embodiments, the compound used in the methods of the present disclosure may be the compound of **Formula IV**:



Formula IV

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula IV**, is also designated by the present disclosure as compound #1.

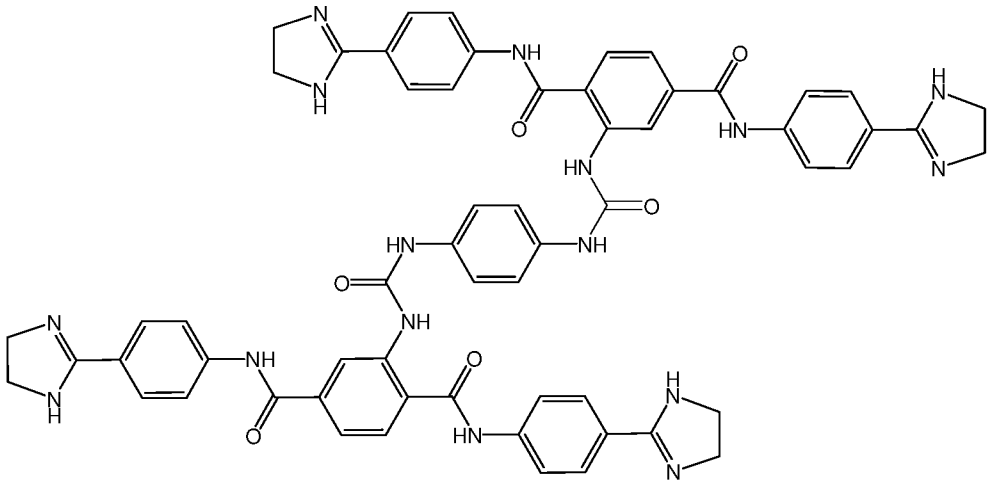
Still further, in some embodiments, the compound used in the methods of the present disclosure may be the compound of **Formula V**:



Formula V

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula V**, is also designated by the present disclosure as compound #3).

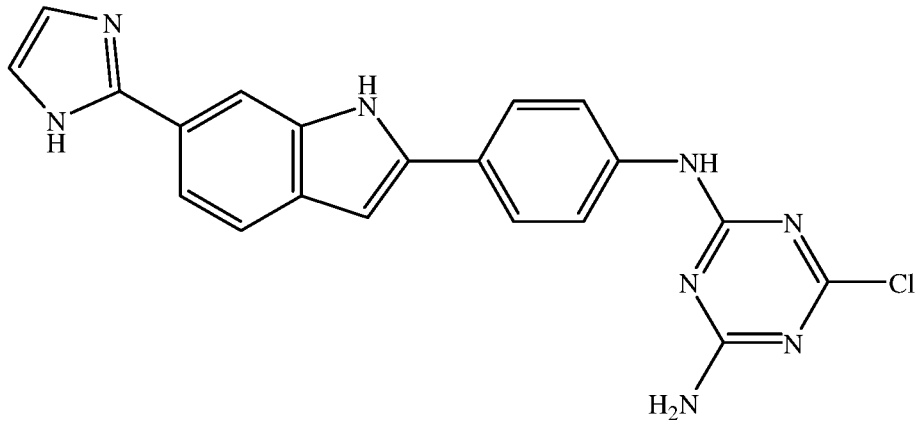
In some further embodiments, the compound used in the methods of the present disclosure may be the compound of **Formula VI**:



Formula VI

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VI**, is also designated by the preset disclosure as compound #4.

In some specific embodiments, the compound used in the methods of the present disclosure may be the compound of **Formula VII**:



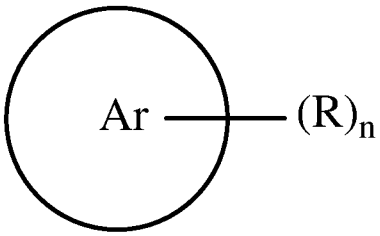
Formula VII

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VII**, is also designated by the present disclosure as compound #6.

As indicated herein, the present disclosure provides a method for inhibiting and/or reducing a metastatic process in a subject. In some embodiments, the metastatic process inhibited by the methods of the invention, may be composed of a multi-step cascade comprising at least one of: tumor cell invasion, entry and cell migration in the blood or lymph vessel system, transmigrating through the circulation and adhering to, extravasate and colonize distal site/s, as discussed herein before, in connection with other aspects of the present disclosure.

In yet some further embodiments, the method disclosed herein results in inhibiting and/or reducing a metastatic process in a subject suffering of a neoplastic malignant disease. More specifically, such disease is at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

Another aspect of the present invention relates to an inhibitory effective amount of at least one small molecule compound for use in a method of inhibiting and/or reducing a metastatic process in a subject in need thereof. In some embodiments, the compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any compositions thereof. More specifically, **Formula I** is:

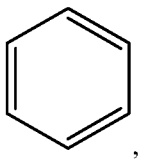


Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In some embodiments, Ar of the compound for use in the present disclosure is selected from the group consisting of:

a)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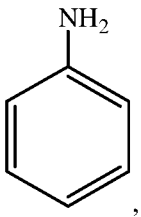
b)



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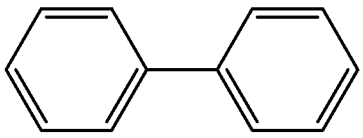
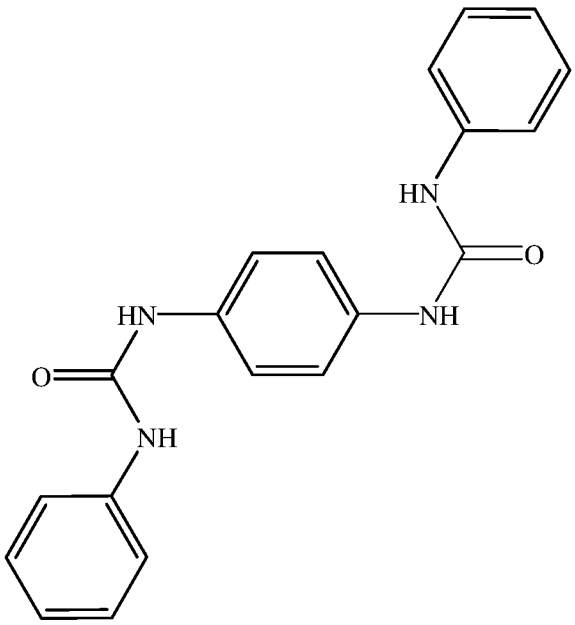
c)


, and

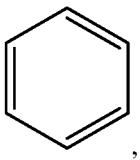
d)



wherein in anyone of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)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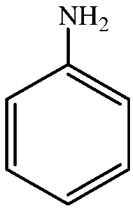
b)



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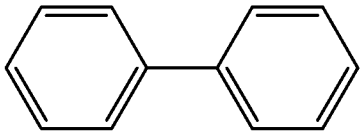
c)



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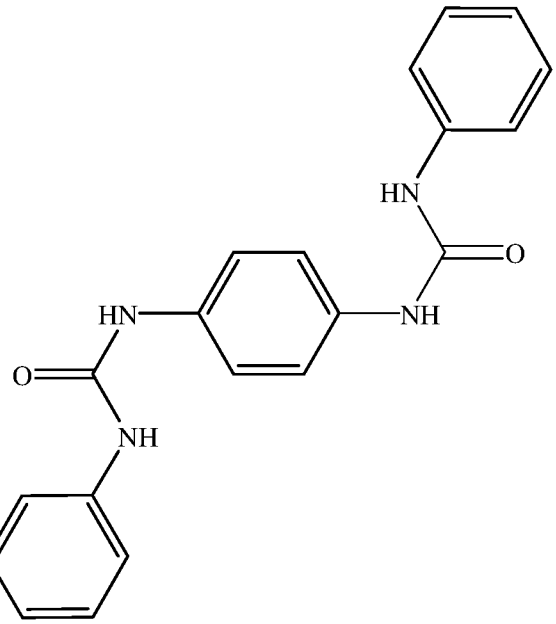
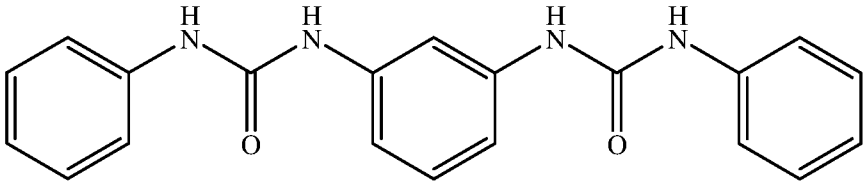
d)



, and

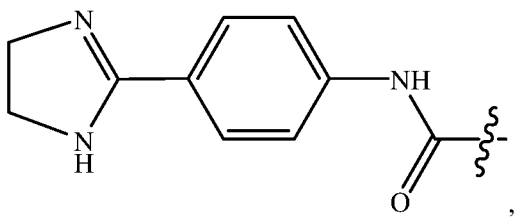
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In yet some further embodiments, the R of the at least one small molecule compound of Formula I for use in the present invention, may be selected from the group consisting of:

a)



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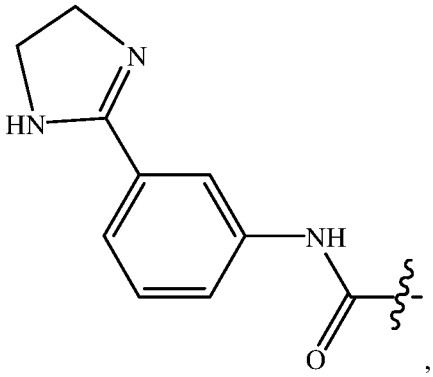
b)



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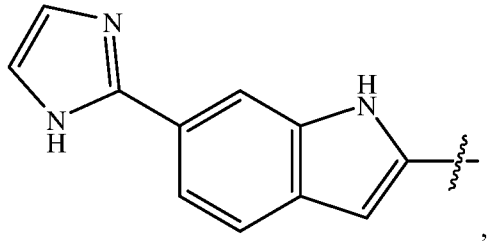
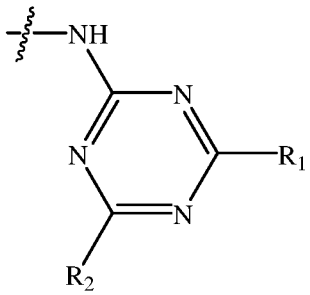
c)



, and

d)

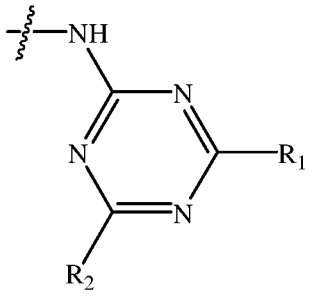


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, -NH_2, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

and wherein each of said R may optionally be further substituted.

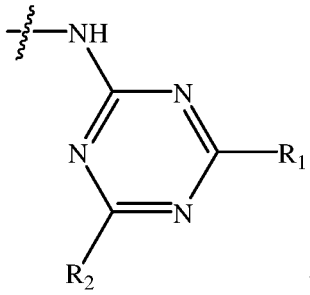
In some embodiments each of said R is not further substituted.

In some embodiments at least one of R is

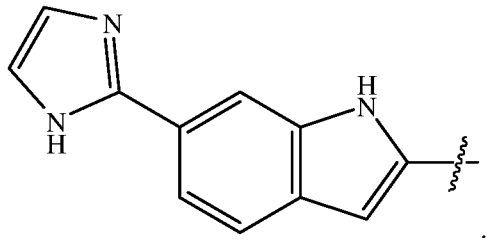


wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$. In some specific embodiments of the method of the present disclosure, at least one of the R is an imidazole derivative and a triazine derivative.

In some embodiments at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



In some specific embodiments, the at least one of the R for use in the method of the present disclosure, is an imidazole derivative.

In some specific embodiments of the method of the present disclosure, the at least one of the R is a dihydroimidazole derivative.

In some specific embodiments of the method of the present disclosure, at least one of the R is a dihydroimidazole derivative.

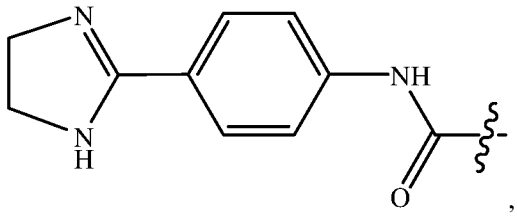
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative which may be the same or different.

In some further specific embodiments, the R of the compound for use in the methods of the present disclosure, may be repeated n times. In some embodiments, n may be 2, 3, or 4.

In some specific embodiments of the method of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



, or

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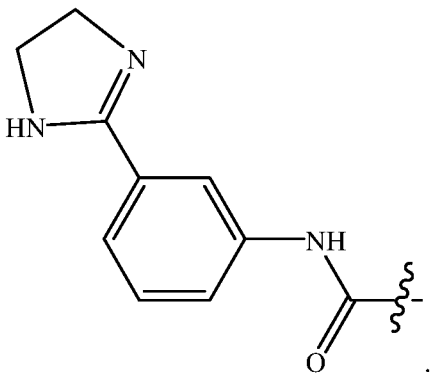

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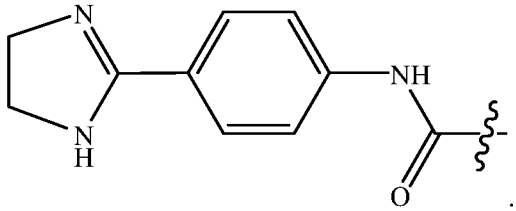
In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



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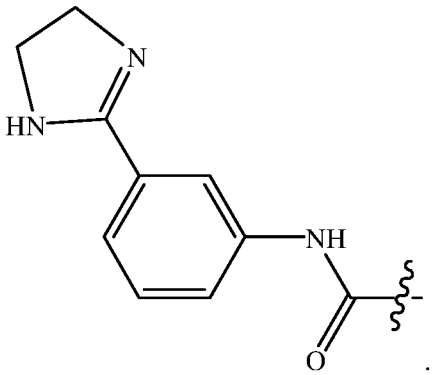
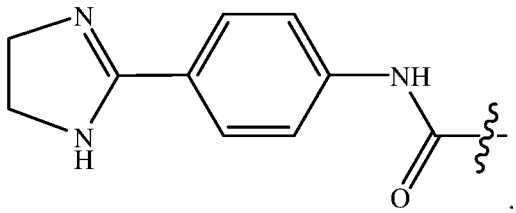
In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



.

In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



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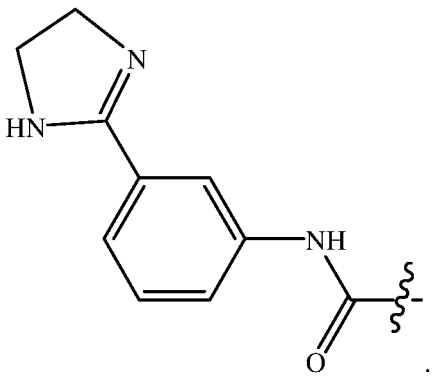
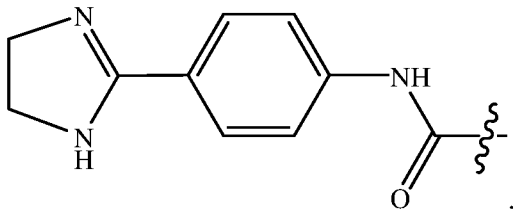
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative

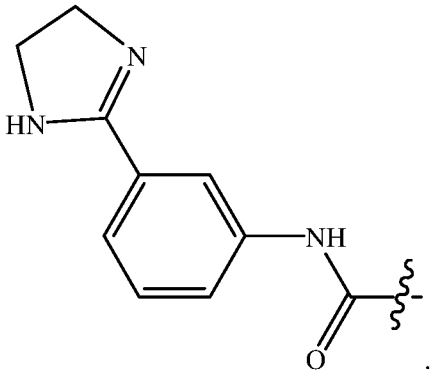


.

In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



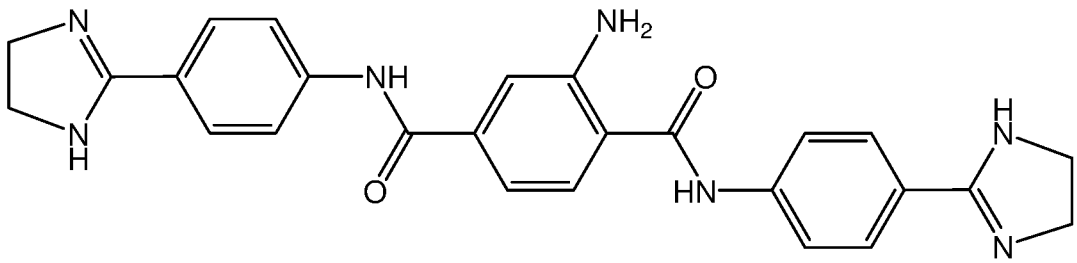
In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



In some embodiments, the at least one small molecule compound of Formula I for use in the methods of the present disclosure may be the compound of any one of **Formula III**, **IV**, **V**, **VI** and **VII**, any salt thereof and any combinations thereof.

In yet some specific embodiments, the at least one small molecule compound of Formula I for use in the present disclosure may be the compound of **Formula III**.

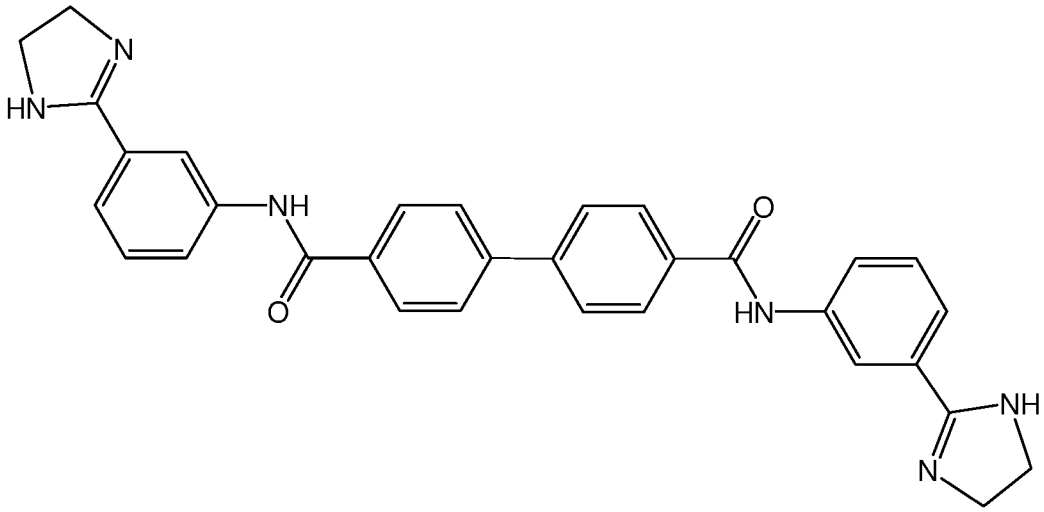
More specifically, the compound of **Formula III** is:



Formula III

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula III**, is also designated by the present disclosure as compound #2.

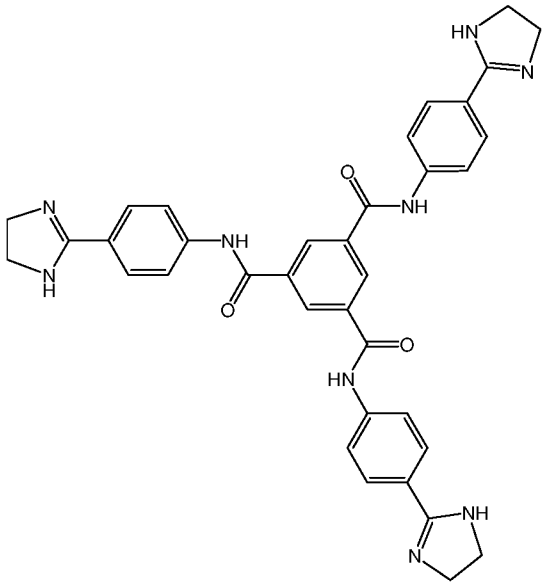
In yet some further embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula IV**. More specifically, the compound of **Formula IV** is:



Formula IV

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula IV**, is also designated by the present disclosure as compound #1.

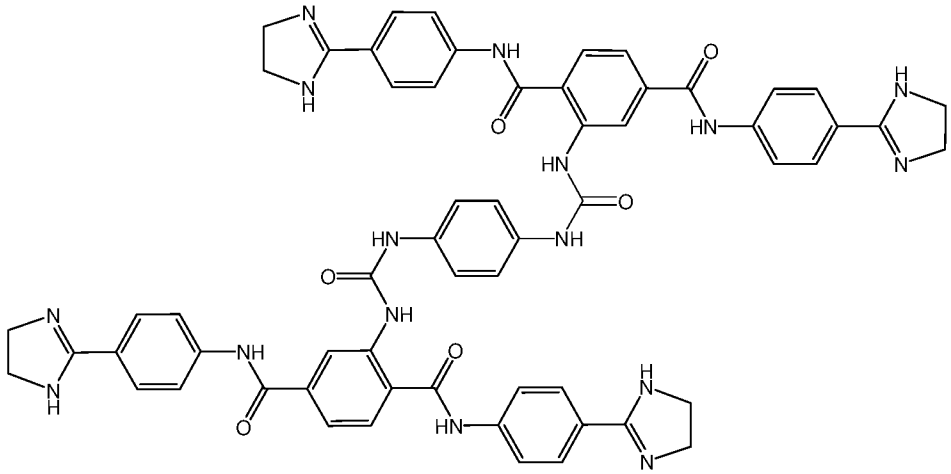
In some further embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula V**. More specifically, the compound of **Formula V** is:



Formula V

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula V**, is also designated by the present disclosure as compound #3.

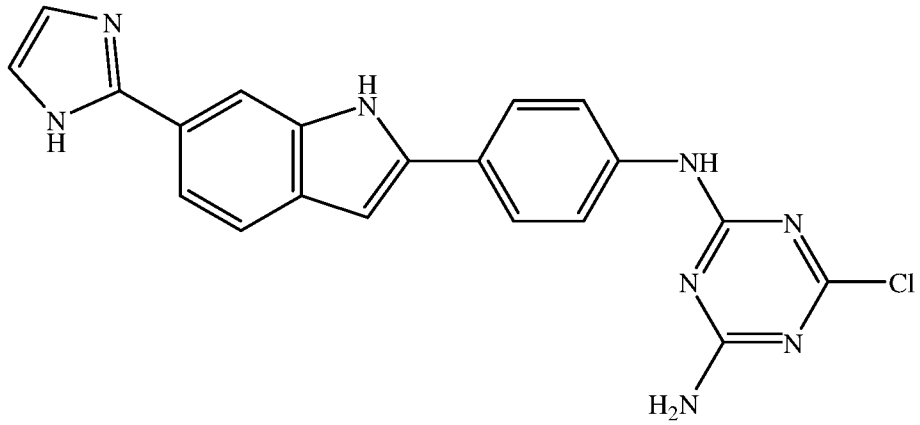
Still further, in some embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula VI**. More specifically, the compound of **Formula VI** is:



Formula VI

a salt thereof, any conjugates thereof. As used herein, this compound of **Formula VI**, is also designated by the present disclosure as compound #4.

Yet in some further embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula VII**. More specifically, the compound of **Formula VII** is:



Formula VII

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VII**, is also designated by the present disclosure as compound #6.

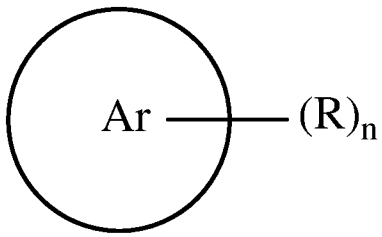
In some embodiments, the metastatic property reduced by the method of the present disclosure, may be at least one of cell invasiveness, cell motility, cell migration and cell adhesion.

In some embodiments, the method of the present disclosure reduces the at least one metastatic property of at least one cell that may be a mammalian malignant cancer cell.

In some embodiments, the methods of the present disclosure led to reduction in the at least one metastatic property of at least one mammalian malignant cancer cell originated from at least one of breast tissue, bladder tissue, kidney tissue, hepatic tissue, pancreatic tissue, colorectal tissue, gastric tissue, lung tissue, skin tissue, ovarian tissue, prostate tissue, thyroid tissue, cervical tissue, endometrium tissue, bone tissue, laryngeal tissue and hematopoietic tissue.

In another aspect, the present disclosure provides a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject. More specifically, the method comprises the step of administering to the subject a therapeutically effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate,

hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof, or any composition thereof. More specifically, **Formula I** is:

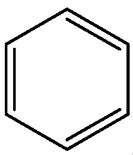


Formula I

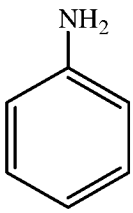
wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In some embodiments of the method disclosed herein, Ar of the compound used, is selected from the group consisting of:

a)

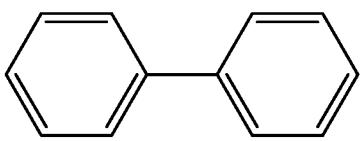

,

b)

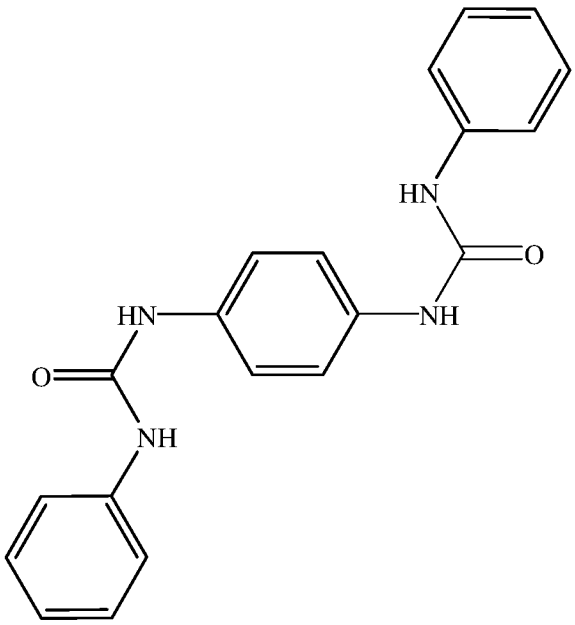


,

c)


, and

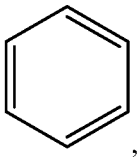
d)



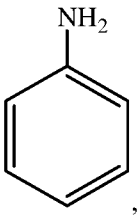
wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)

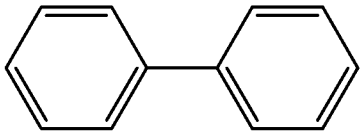

,

b)



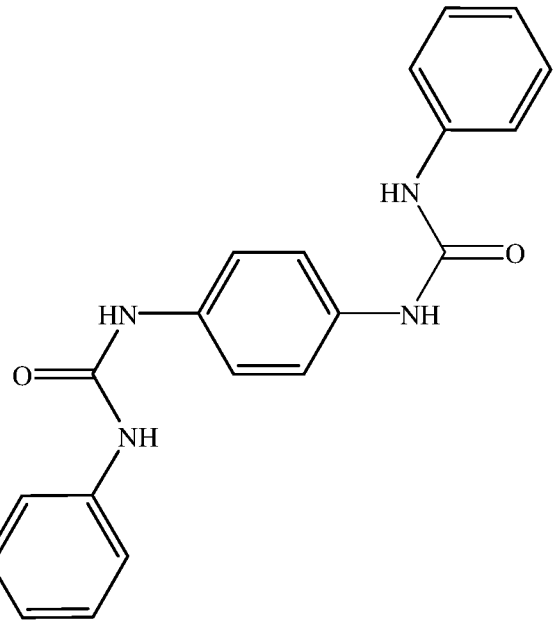
,

c)



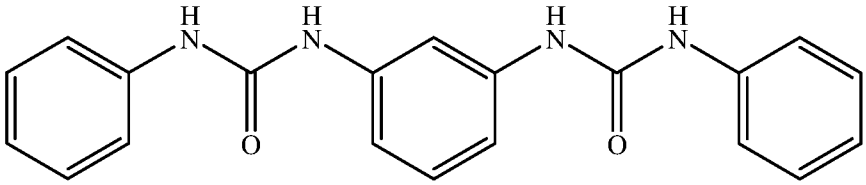
,

d)



, and

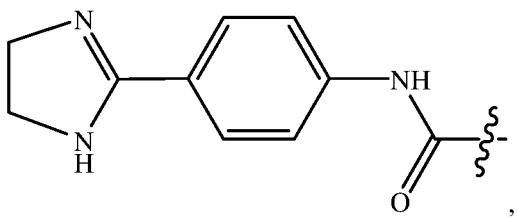
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

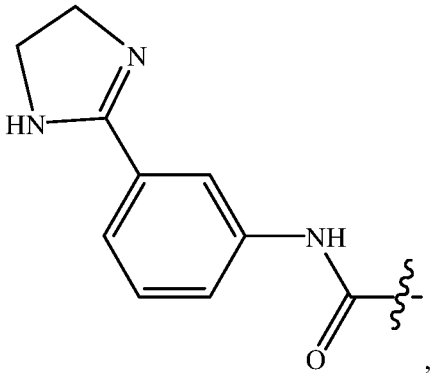
In some further embodiments, R of the compounds used by the methods disclosed herein, is selected from the group consisting of:

a)



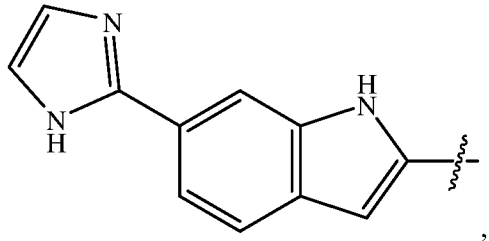
,

b)



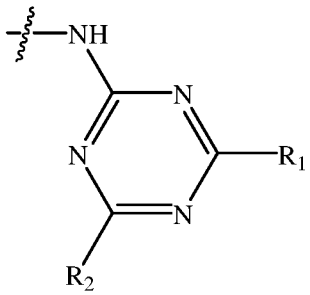
,

c)



, and

d)

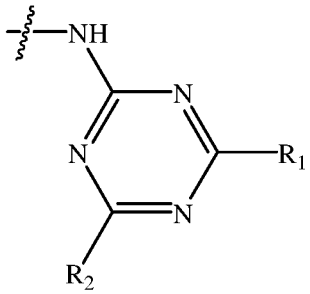


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, -NH_2, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

and wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

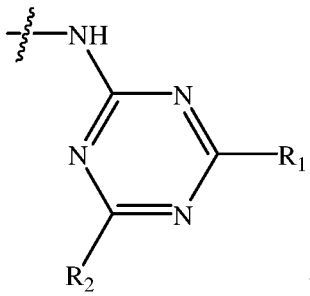
In some embodiments at least one of R is



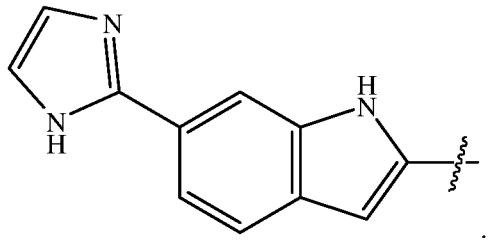
wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$.

In some specific embodiments of the method of the present disclosure, at least one of the R is an imidazole derivative and a triazine derivative.

In some embodiments at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



In some embodiments, at least one of the t R of the compounds used by the methods of the invention, is an imidazole derivative.

In some specific embodiments of the method of the present disclosure, the at least one of the R is a dihydroimidazole derivative.

In some specific embodiments of the method of the present disclosure, at least one of the R is a dihydroimidazole derivative.

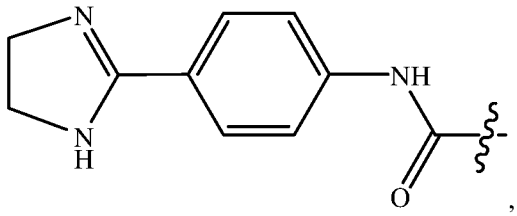
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative which may be the same or different.

In some specific embodiments, the R of the compounds used by the methods of the present disclosure may be repeated n times (either identical or different R), wherein n is 2, 3, or 4.

In some specific embodiments of the method of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

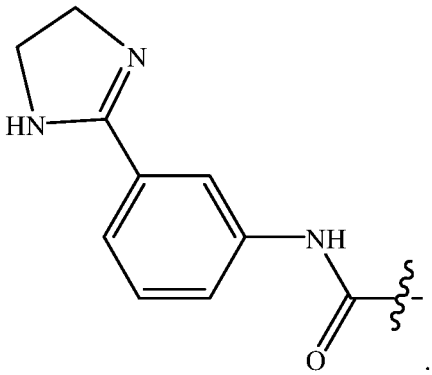
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



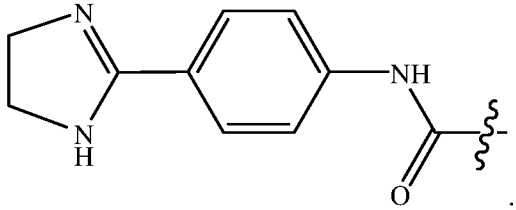
, or

b)



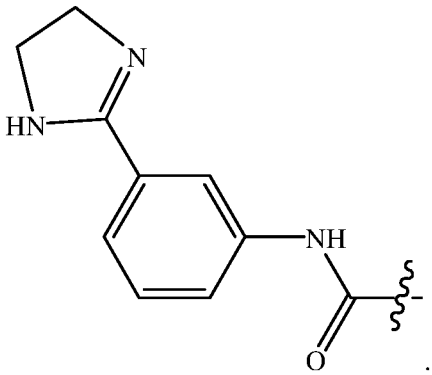
.

In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



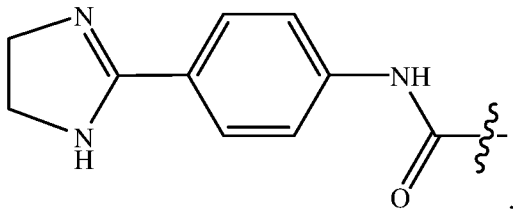
.

In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



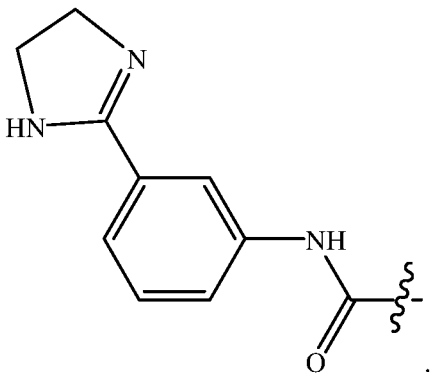
.

In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



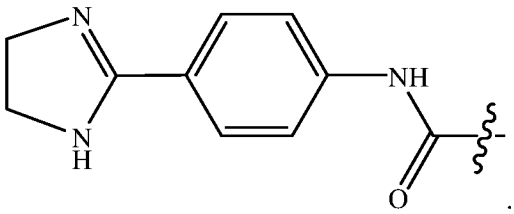
.

In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative

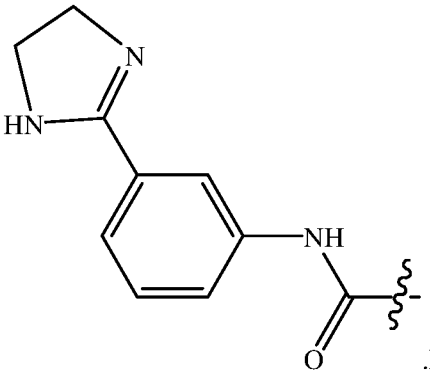


.

In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative

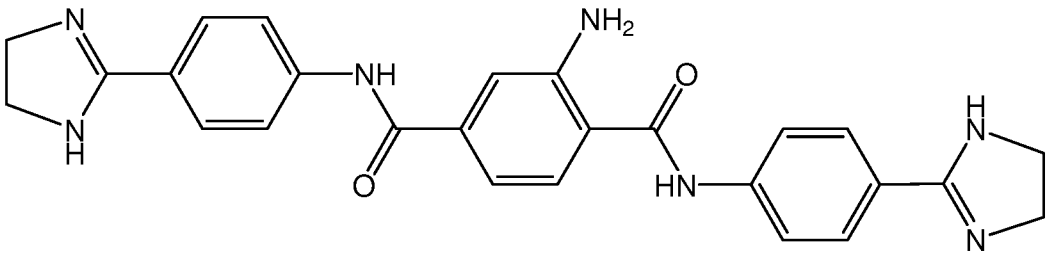


In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



.In some embodiments, compound used by the methods of the present disclosure is the compound of at least one of, **Formulas III**, **IV**, **V**, **VI** and/or **VII**, and any combinations thereof.

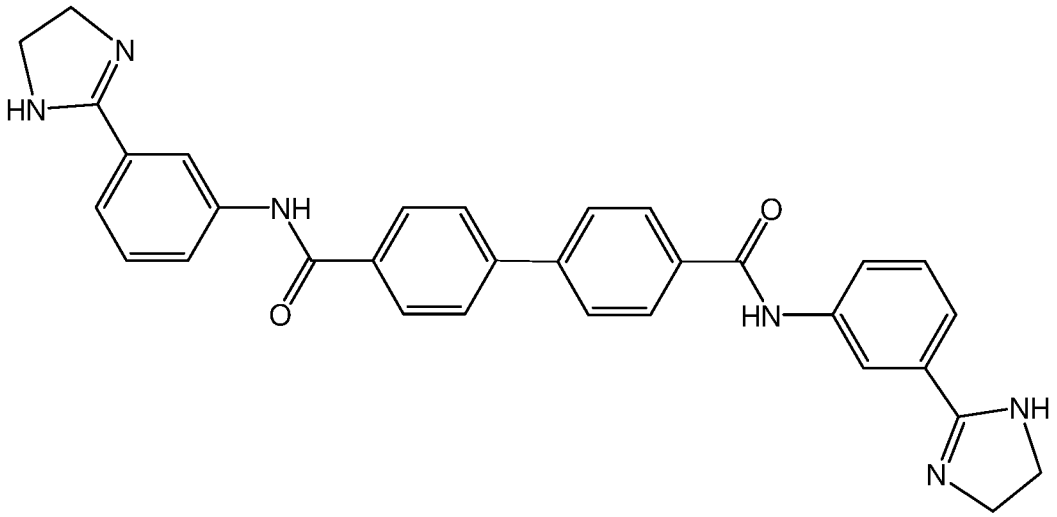
In some further embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula III**:



Formula III

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula III**, is also designated by the present disclosure as compound #2.

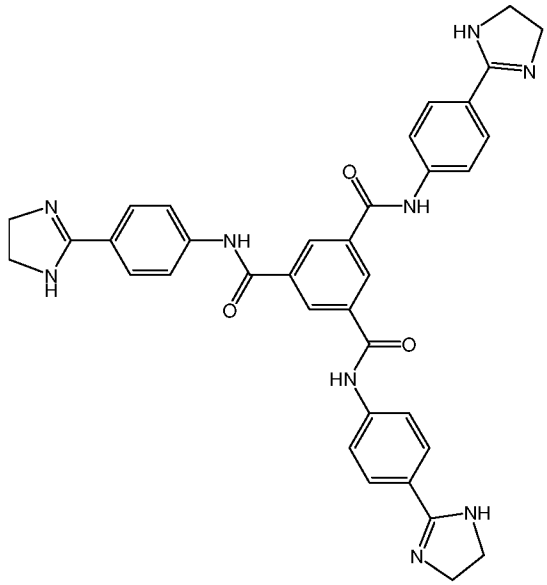
Yet in some further embodiments, the at least one small molecule compound of Formula I used in the methods of the present disclosure may be the compound of **Formula IV**:



Formula IV

a salt thereof, any conjugates thereof. As used herein, this compound of **Formula IV**, is also designated by the present disclosure as compound #1.

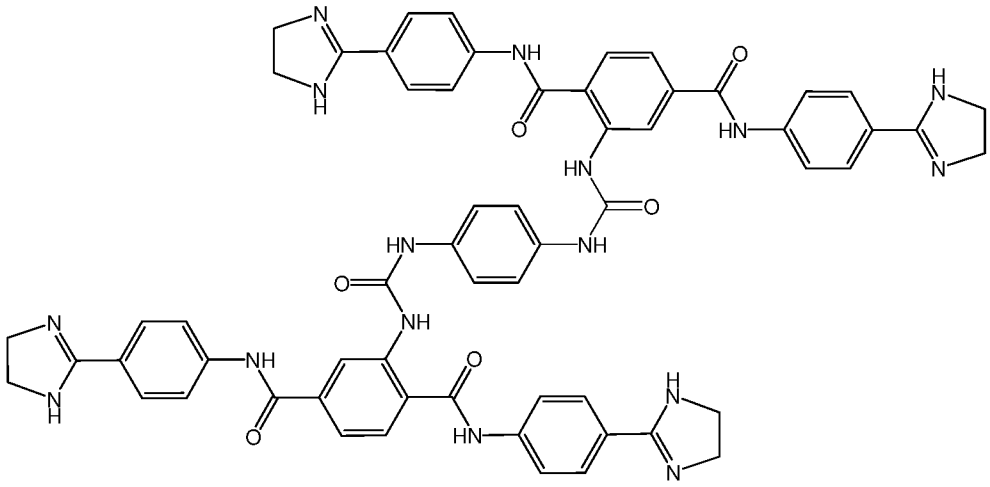
In some further embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula V**:



Formula V

a salt thereof, any conjugates thereof. As used herein, this compound of **Formula V**, is also designated by the present disclosure as compound #3.

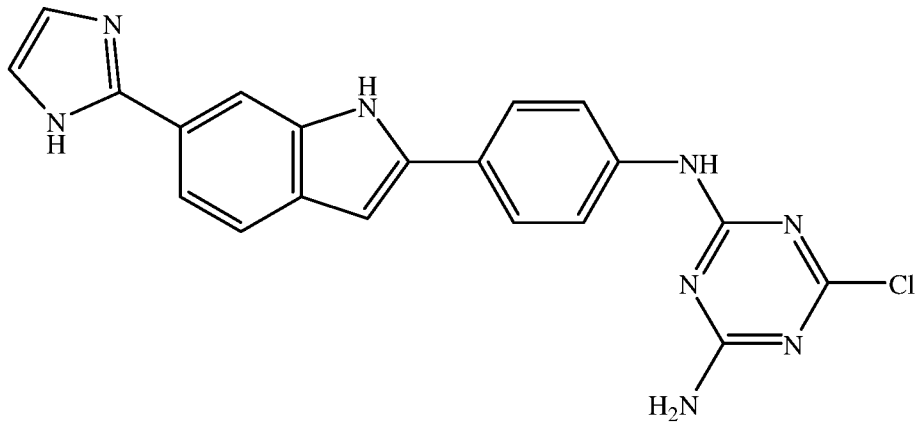
Still further, in some embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula VI**:



Formula VI

a salt thereof, any conjugates thereof. As used herein, this compound of **Formula VI**, is also designated by the present disclosure as compound #4.

Yet in some further embodiments, the at least one small molecule compound of Formula I used in the methods of the present disclosure may be the compound of **Formula VII**:



Formula VII

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VII**, is also designated by the present disclosure as compound #6.

In some embodiments, the method disclosed herein is applicable for treating a neoplastic disorder. In some embodiments, the proliferative malignant disease or disorder may be at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, specifically, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

In some further embodiments, the proliferative malignant disease treated by the methods of the present disclosure is a metastatic disease originated from a primary and/or secondary proliferative malignant disease, said proliferative malignant disease is at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

The term **"proliferative disorder"** used in this invention to collectively refer to malignant diseases and/or any other non-cancerous diseases that may be characterized by benign neoplasia, benign tumor or hyperplasia of a tissue or organ. **Non-cancerous proliferative conditions** are characterized by abnormal cell division, cells that divide faster than normal and/or without control however do not metastasize. Such conditions include but are not limited to hemangiomas and psoriasis. However, some non-cancerous proliferative conditions such as adenoma are considered as actually **pre-cancerous conditions** because of the risk of transforming into a malignant disease - adenocarcinoma. To remove any doubt, the term "**proliferative disorder**" as used the present disclosure, include malignant diseases, non-cancerous diseases, and pre-cancerous conditions. As used herein, the terms "**disease", "disorder", "condition**" relates to a subject's health, and are used interchangeably and have meanings ascribed to each and all of such terms.

Still further, in some embodiments, malignant disease is a metastatic disease originated from a **"primary and/or secondary tumors"**. Thus, the compounds of the present disclosure my be applicable for any metastatic condition that may be originated from any primary and/or secondary tumor. As implied herein, metastases can originate from a primary malignant tumor, but can also originate from malignant tumor cells residing in a secondary site/tumor. When being characterized under a microscope and in other

ways, metastatic cancer cells have features like that of the primary cancer and not like the cells in the tissue where the metastatic cancer is found. For this reason, metastatic cancer has the same name as the primary cancer. For example, lung cancer that spreads to the bone is called metastatic lung cancer, not bone cancer, and is treated as stage IV lung cancer. **"primary and/or secondary tumors"** to the bone, liver, and lung. **Breast** cancers metastasize to the bone, brains, liver, and lung. **Colon** cancers metastasize to the liver, lung, and peritoneum. **Kidney** cancers metastasize to the adrenal gland, bone, brain, liver, and lung. **Lung** cancers metastasize to the adrenal gland, bone, brain, liver, and lung. **Melanoma** cancers metastasize to the bone, brain, liver, lung, skin, and muscle. **Ovarian** cancers metastasize to the liver, lung, and peritoneum. **Pancreatic** cancers metastasize to the liver, lung, and peritoneum. **Prostate** cancers metastasize to the adrenal gland, bone, liver, and lung. **Rectal** cancers metastasize to the liver, lung, and peritoneum. **Gastric** cancers metastasize to the liver, lung, and peritoneum. **Thyroid** cancers metastasize to the bone, liver, and lung. **Uterus** cancers metastasize to the bone, liver, lung, peritoneum, and vagina. **Bladder cancer** metastasize to the lymph nodes, bones, lung, liver, and peritoneum. **Cervical cancer** metastasize to the lungs. **Leukemia and lymphoma** cancers can metastasize to the central nervous system, lungs, heart and liver.

In some embodiments, the disclosed method may be particularly applicable for a primary, an/or a secondary proliferative malignant disease that exists in a dormant, inactive state.

Cancer Dormancy or **"proliferative malignant disease that exists in a dormant, inactive state"** in relation to the method disclosed herein, refers to the phenomenon of **"cellular dormant"** or **"dormant tumor cells",** very early during tumor progression, cancer cells may leave the primary location and travel to a secondary location/s. These disseminated cells can remain inactive (that is, dormant or quiescent) and asymptomatic for months, years, or even decades. **Quiescence** is the state where cells are not dividing but at arrest in the cell cycle in G0-G1. At some point, these dormant metastatic cells, can start to grow. Most existing cancer treatments are thought to only target dividing cells, not dormant ones.

It should be appreciated that the compounds of the present disclosure and any combinations thereof, are applicable for any malignant disorder that display expression (or increased expression) of the KAI1 as-lncRNA, and/or decreased expression of the

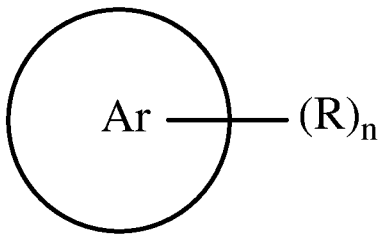
KAI1/CD82, as discussed herein after in connection with other aspects of the present disclosure.

As specifically being directed a metastatic features of cancer cells, the small molecule compounds of any one of **Formulas I** to **VII** disclosed herein, may be used for treating the disclosed metastatic disorders. In yet some further embodiments, the disclosed compounds may be combined with anti-proliferative therapy (e.g., anti-proliferative drugs and procedures), thereby providing a combined therapeutic approach.

Thus, in some further embodiments, the subject treated by the methods disclosed herein, is further treated with at least one anti-proliferative therapy (e.g., drugs and/or procedures), prior to, after, and/or simultaneously with the administration of the at least one small molecule compound.

In some embodiments, the anti-proliferative therapy may comprise at least one of chemotherapy, radiosurgery, radiation therapy, biological therapy, immune-therapy, hormone therapy, surgery, or any combination thereof. In some embodiments, the anti-proliferative therapy is aimed at treating the primary, secondary tumors, or combination thereof. The combined therapy disclosed herein will be elaborated herein after in connection with other aspects of the invention.

In another aspect, the present invention provides an inhibitory effective amount of at least one small molecule compound for use in a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject. In some embodiments, the compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof. More specifically, **Formula I** is:



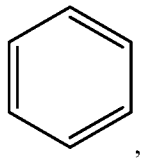
Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be

further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In some embodiments, Ar of the compound for use in the present disclosure is selected from the group consisting of:

a)



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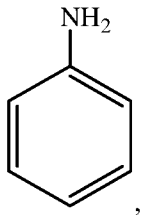
b)



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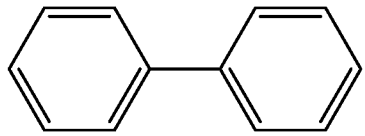
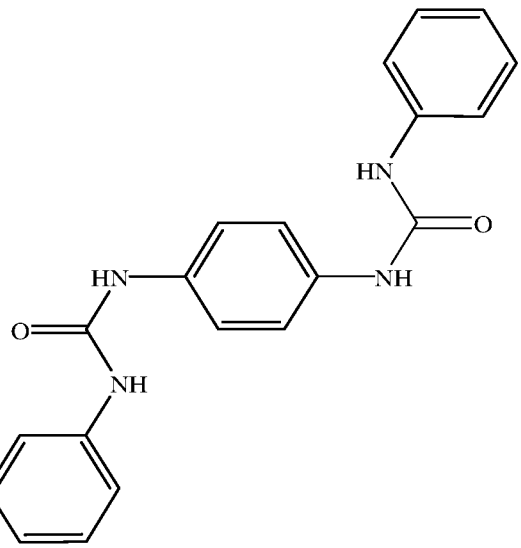
c)



, and

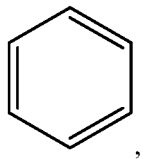
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some embodiments of the compound for use of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)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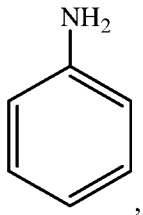
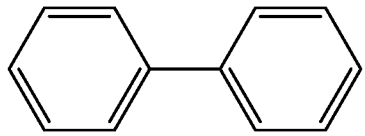
b)



,

c)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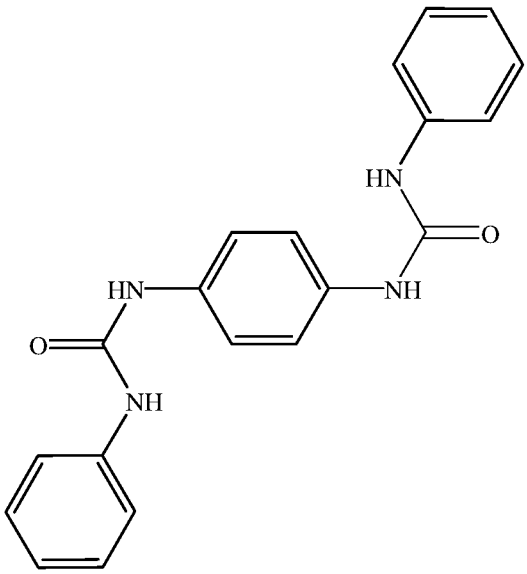
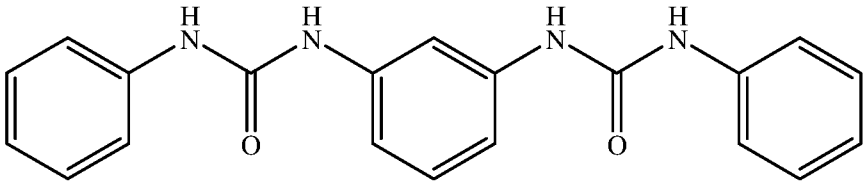
d)



, and

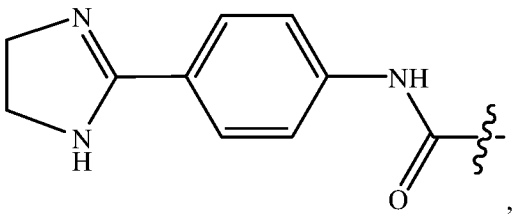
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

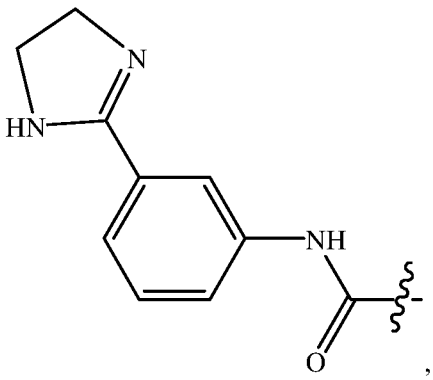
In yet some further embodiments, the R of the compounds for use in the present invention, may be selected from the group consisting of:

a)



,

b)



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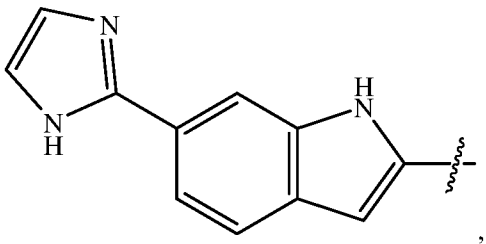
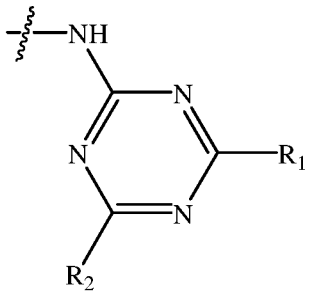
c)



, and

d)

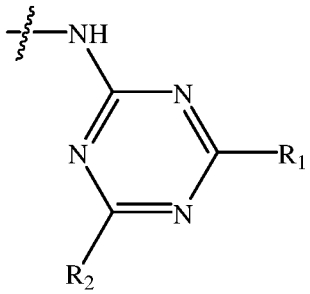


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, -NH_2, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

and wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

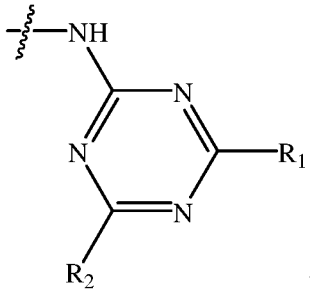
In some embodiments at least one of R is



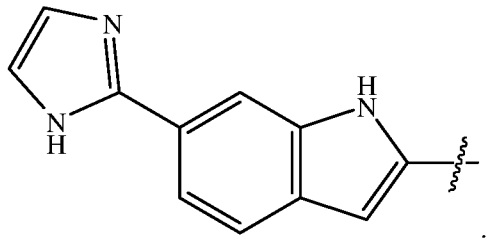
wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$.

In some specific embodiments of the compound for use of the present disclosure, at least one of the R is an imidazole derivative and a triazine derivative.

In some embodiments at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



.

In some specific embodiments, the at least one of the R for use in the method of the present disclosure, is an imidazole derivative.

In some specific embodiments of the compound for use of the present disclosure, the at least one of the R is a dihydroimidazole derivative.

In some specific embodiments of the compound for use of the present disclosure, at least one of the R is a dihydroimidazole derivative.

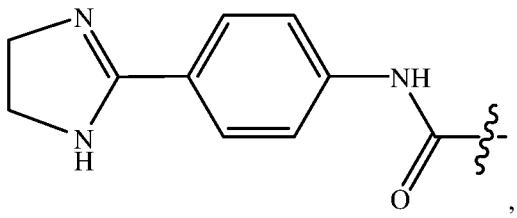
In some specific embodiments of the compound for use of the present disclosure, R is one or more dihydroimidazole derivative which may be the same or different.

In some further specific embodiments, the R of the compound for use in the methods of the present disclosure, may be repeated n times (either identical or different). In some embodiments, n may be 2, 3, or 4.

In some specific embodiments of the compound for use of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

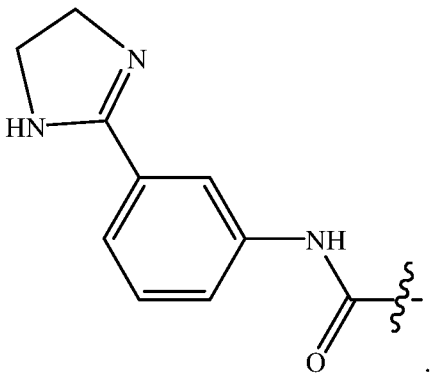
In some specific embodiments of the compound for use of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



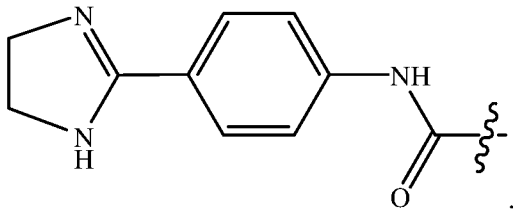
, or

b)



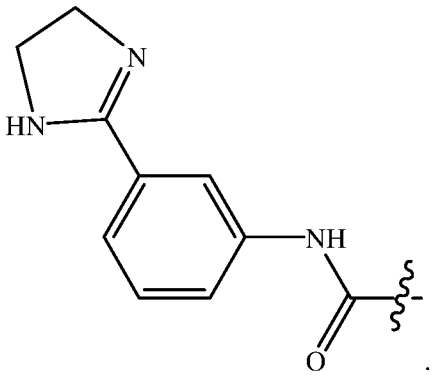
.

In some specific embodiments of the compound for use of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative

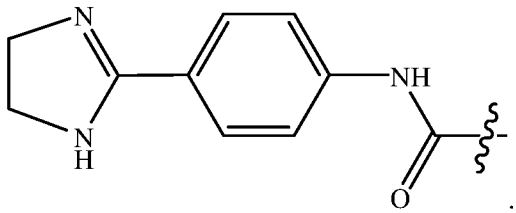


.

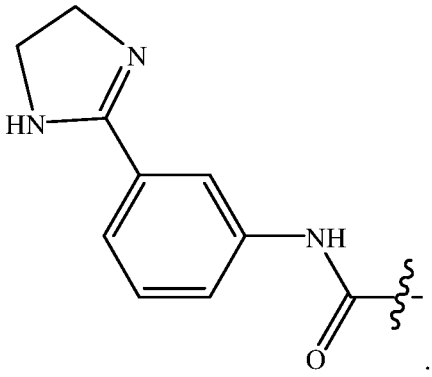
In some specific embodiments of the compound for use of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



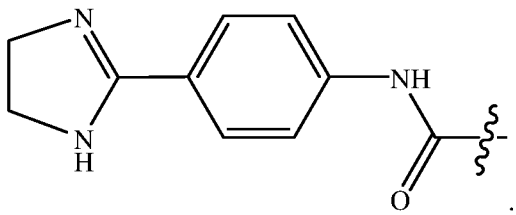
In some specific embodiments of the compound for use of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



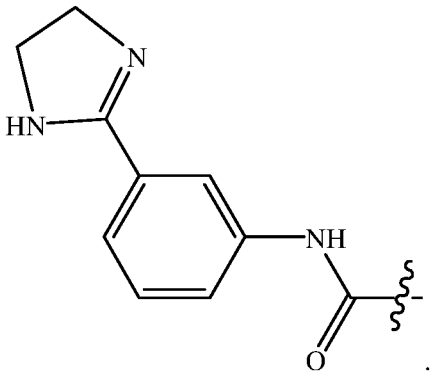
In some specific embodiments of the compound for use of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



In some specific embodiments of the compound for use of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative

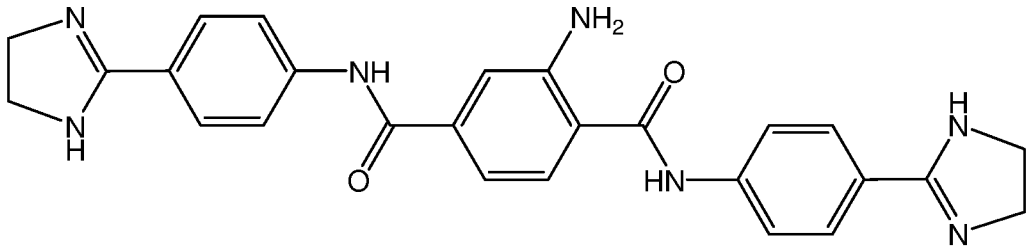


In some specific embodiments of the compound for use of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



In some embodiments, compound for use by the methods of the present disclosure is the compound of at least one of, **Formulas III**, **IV**, **V**, **VI** and/or **VII**, and any combinations thereof.

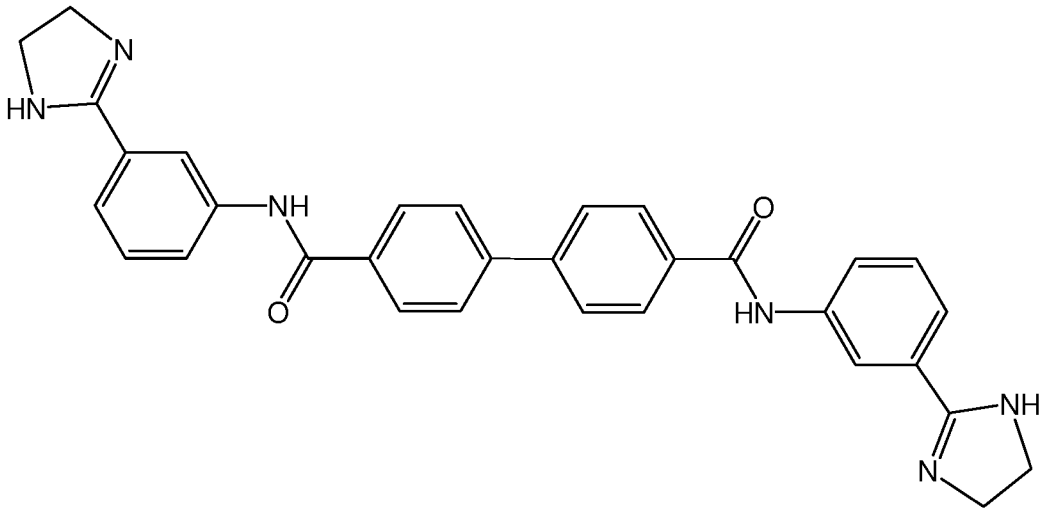
In some further embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula III**:



Formula III

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula III**, is also designated by the present disclosure as compound #2.

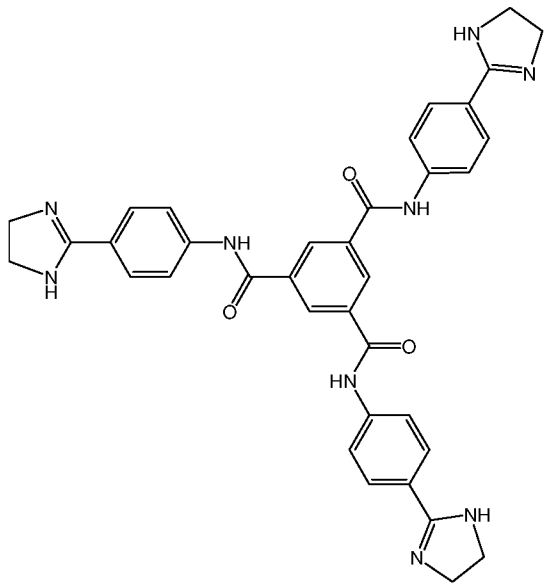
Yet in some further embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula IV**:



Formula IV

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula IV**, is also designated by the present disclosure as compound #1.

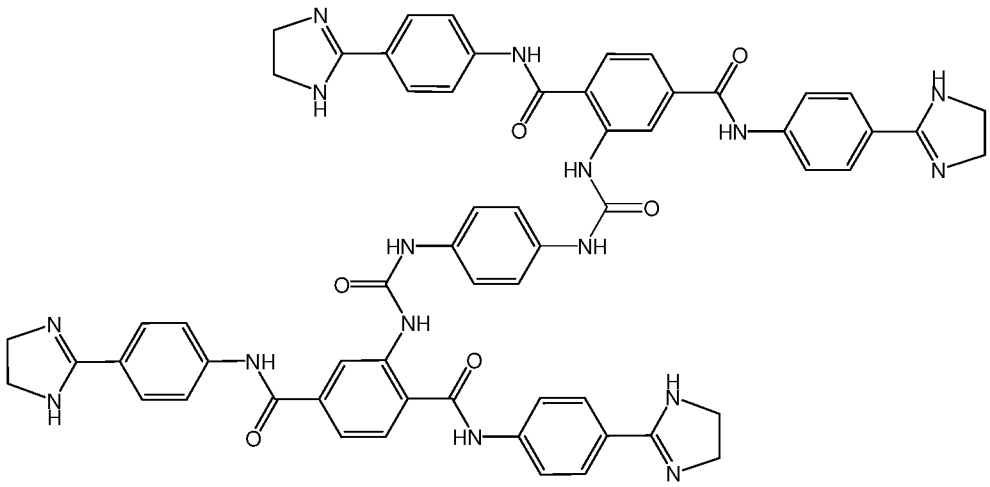
In some further embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula V**:



Formula V

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula V**, is also designated by the present disclosure as compound #3.

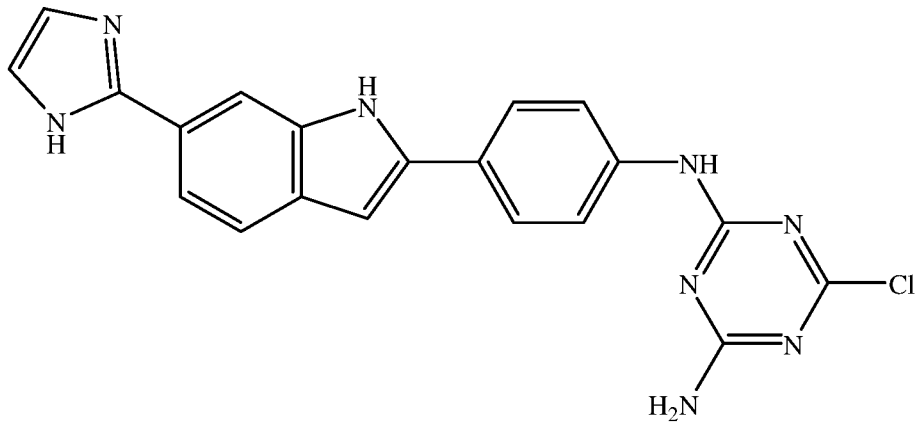
Still further, in some embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula VI**:



Formula VI

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VI**, is also designated by the present disclosure as compound #4.

Yet in some further embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula VII**:



Formula VII

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VII**, is also designated by the present disclosure as compound #6.

In some embodiments, the small molecule compounds for use disclosed herein are applicable for treating a proliferative malignant disorder. In some embodiments, the proliferative malignant disease or disorder may be at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, specifically, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

In some further embodiments, the compounds for use of the present disclosure are applicable for treating a proliferative malignant disease that is a metastatic disease originated from a primary and/or secondary proliferative malignant disease, said proliferative malignant disease is at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

In some embodiments, the compounds for use disclosed herein are applicable for treating a primary proliferative malignant disease that exists in a dormant, inactive state.

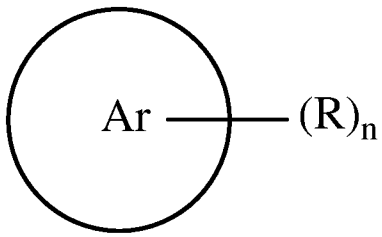
In some further embodiments, the subject treated by the compounds used in the methods disclosed herein, is further treated with at least one anti-proliferative therapy, prior to, after, and/or simultaneously with the administration of the at least one small molecule compound.

In some embodiments, the anti-proliferative therapy may comprise at least one of chemotherapy, radiosurgery, radiation therapy, biological therapy, immune-therapy, hormone therapy, surgery, or any combination thereof.

In some embodiments, the anti-proliferative therapy is aimed at treating the primary, secondary tumors, or combination thereof.

In another aspect, the present invention relates to a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject treated with at least one anti-proliferative therapy. More specifically, the method comprises the step of administering to the subject a therapeutically effective amount of at least one small molecule compound of Formula I, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, any

combinations thereof, or any composition thereof, prior to, after, and/or simultaneously with the at least one anti-proliferative therapy. In some embodiments, **Formula I** is:

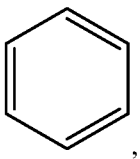


Formula I

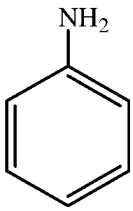
wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In some embodiments, Ar of the compound used by the method of the present disclosure is selected from the group consisting of:

a)


,

b)



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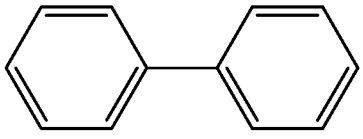
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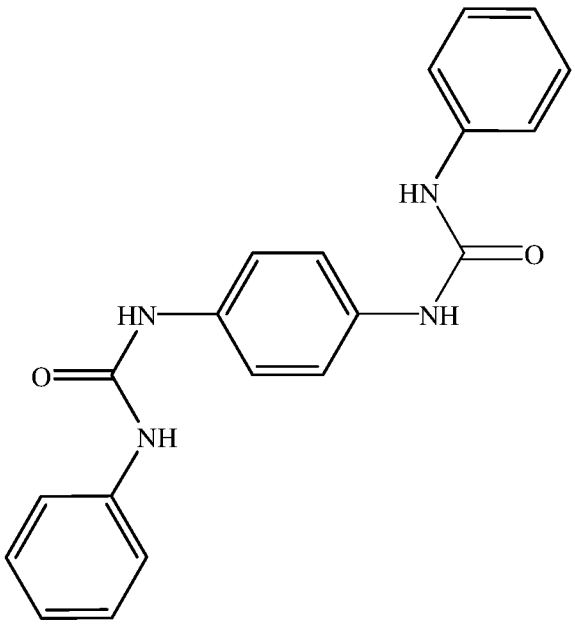
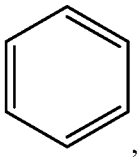
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)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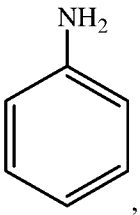
b)



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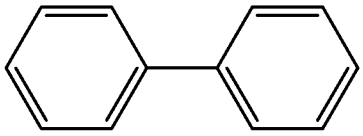

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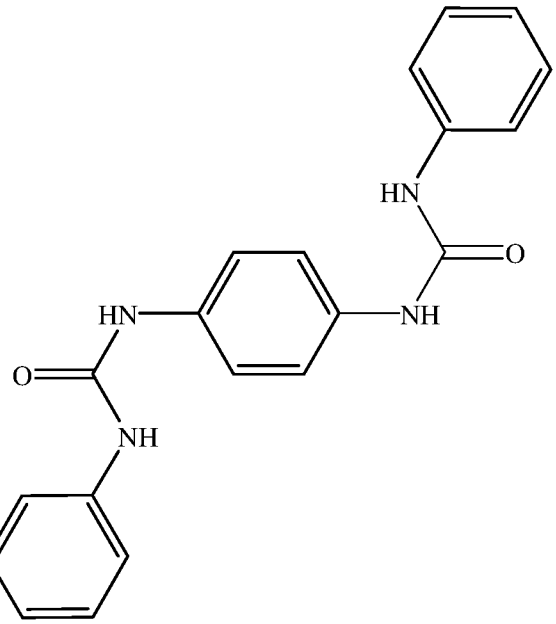

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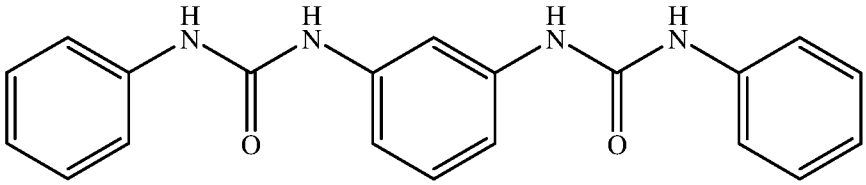
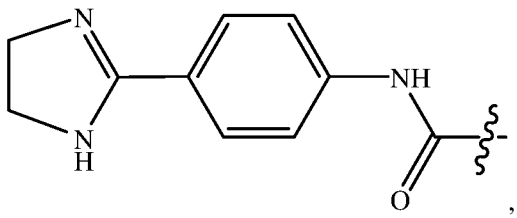


wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some embodiments, R of the compound used by the method of the present disclosure is selected from the group consisting of:

a)



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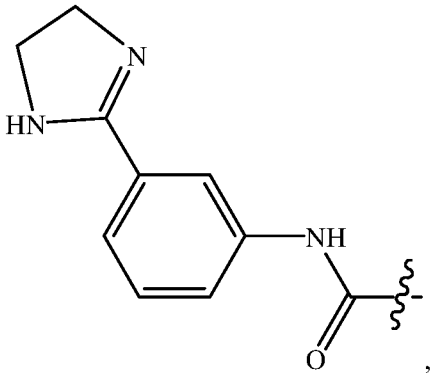

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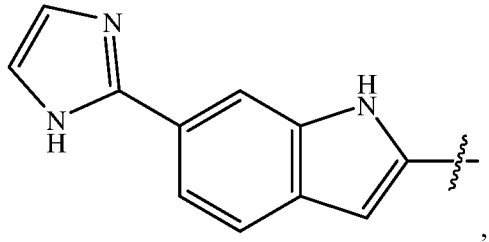

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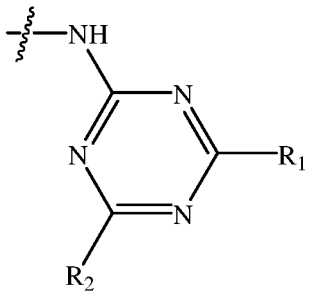
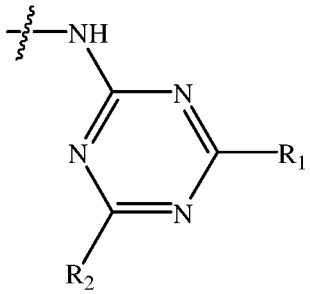


wherein R_1 and R_2 each are independently selected from the group consisting of hydrogen, halogen, -OH, -NH_2, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

and wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

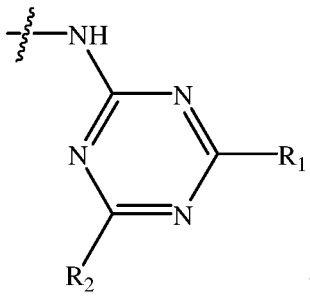
In some embodiments at least one of R is



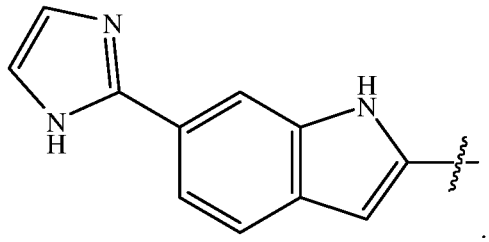
wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$.

In some specific embodiments of the method of the present disclosure, at least one of the R is an imidazole derivative and a triazine derivative.

In some embodiments at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



In some further embodiments, the methods disclosed herein, use a compound comprising an R that is an imidazole derivative.

In some specific embodiments of the method of the present disclosure, the at least one of the R is a dihydroimidazole derivative.

In some specific embodiments of the method of the present disclosure, at least one of the R is a dihydroimidazole derivative.

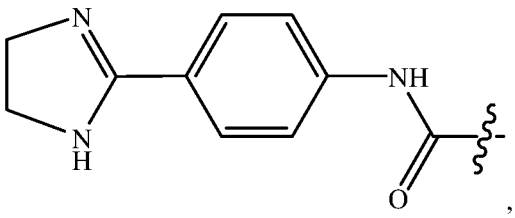
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative which may be the same or different.

In some specific embodiments, the method disclosed herein uses a compound comprising at least one R repeated n times, wherein n is 2, 3, or 4.

In some specific embodiments of the method of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



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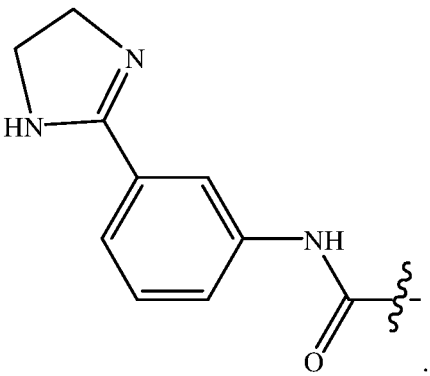

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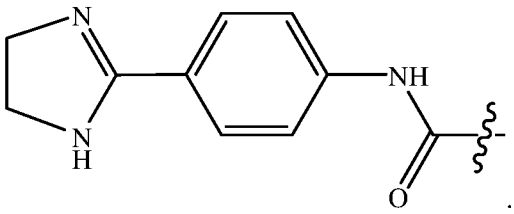
In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



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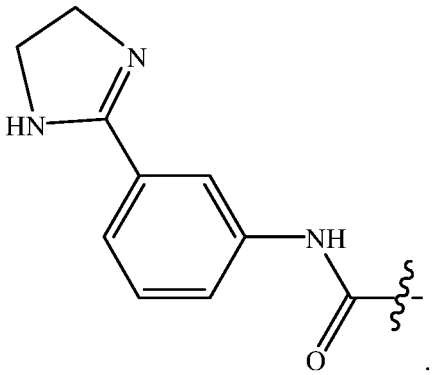
In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



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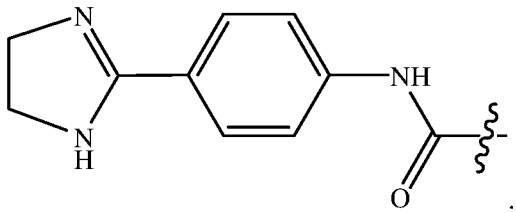
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



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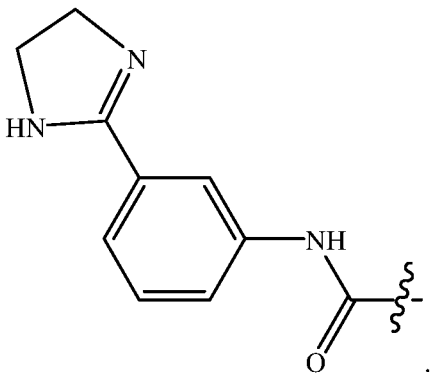
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



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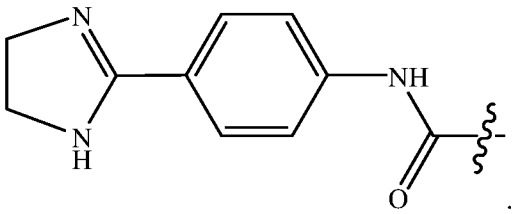
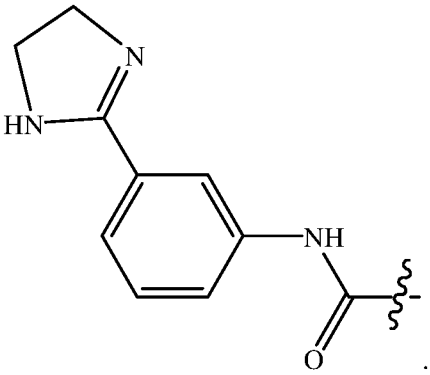
In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative

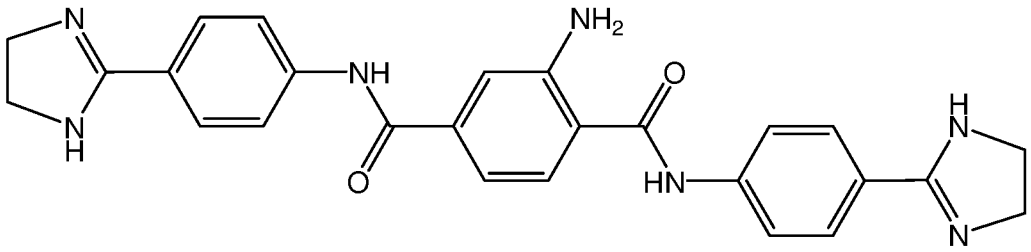


In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



In some embodiments, the therapeutic methods of the present disclosure may use at least one compound of at least one of: **Formulas III**, **I**, **V**, **VI** and/or **VII**, and any combinations thereof.

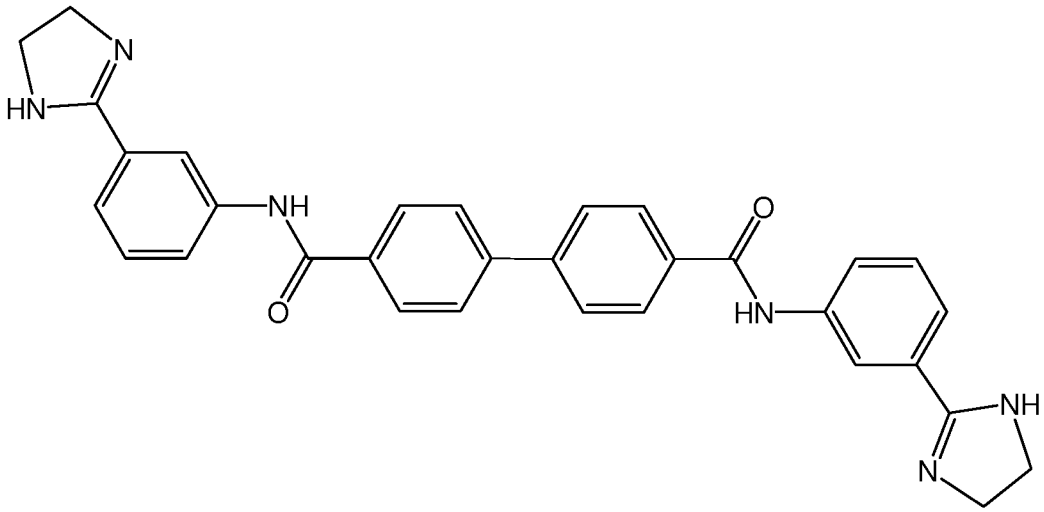
In some embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula III**:



Formula III

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula III**, is also designated by the present disclosure as compound #2.

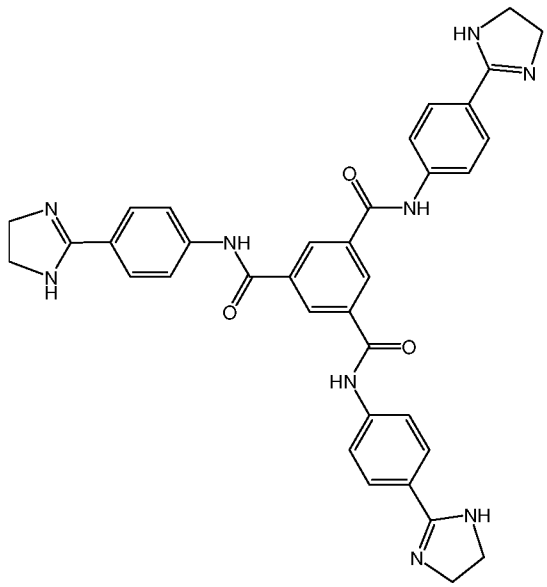
In yet some further embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula IV**:



Formula IV

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula IV**, is also designated by the present disclosure as compound #1.

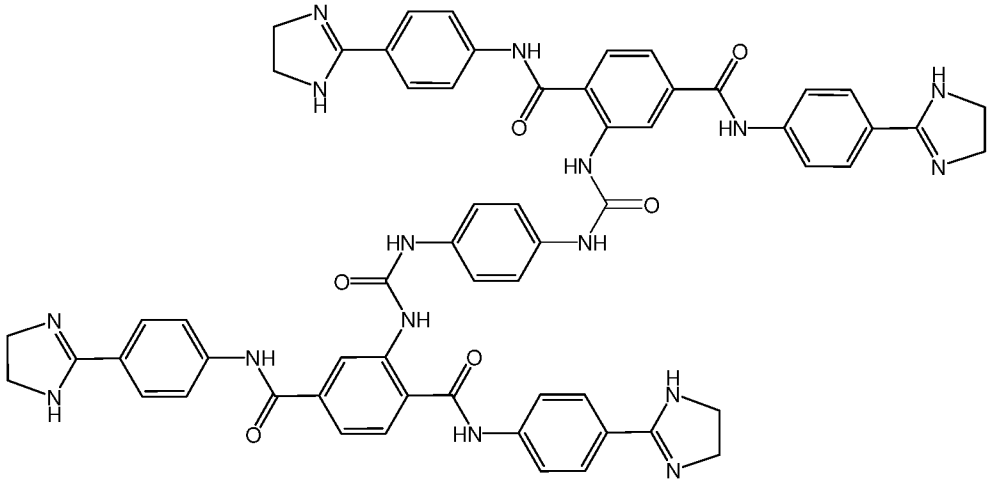
In some further embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula V**:



Formula V

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula V**, is also designated by the preset disclosure as compound #3.

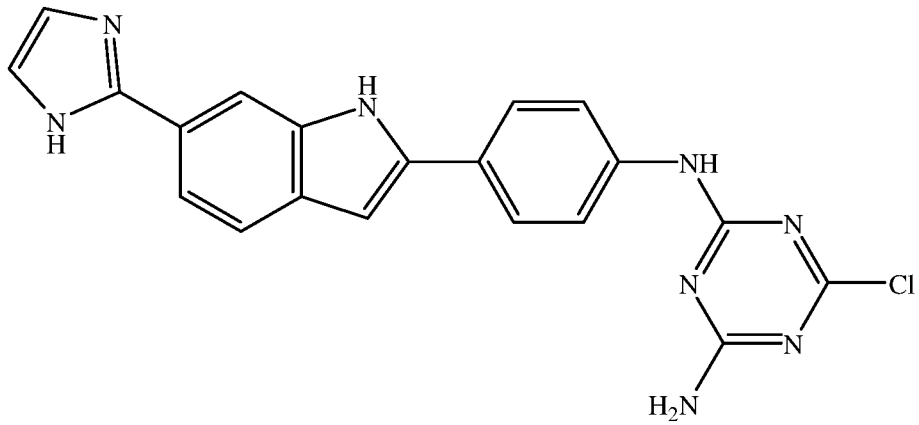
In some further embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula VI**:



Formula VI

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VI**, is also designated by the present disclosure as compound #4.

Still further, in some embodiments, the at least one small molecule compound of **Formula I** used in the methods of the present disclosure may be the compound of **Formula VII**:



Formula VII

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VII**, is also designated by the present disclosure as compound #6.

The method of the present disclosure combines the use of the compounds disclosed herein in the treatment of subjects treated with anti-proliferative and/or anti neoplastic

therapy, that may comprise in some embodiments at least one of chemotherapy, radiosurgery, radiation therapy, biological therapy, immune-therapy, hormone therapy, surgery, or any combination thereof. More specifically, the methods of the preset disclosure may combine the use of the small molecule compounds of any one of **Formulas I** to **VII**, as disclosed herein, as well as any combinations thereof and/or any compositions and formulations thereof, with any anti-proliferative therapy disclosed herein. Thus, in some embodiments, treatment of subject with said small molecule compound modulator is performed prior to, simultaneously, or after administration of an **"Anti-proliferative therapy"**.

The term "**Anti-proliferative therapy**" as used herein refers to any treatment intended for eliminating or destructing (killing) cancer cells or cells of any other proliferative disorder. This includes "chemotherapeutic drugs or agents" (chemotherapy), "targeted therapies", "biological therapy" or "immunotherapy", "radiation therapy", "surgery", "radiosurgery", "hormone therapy".

The following definitions thus relate to "**Anti-proliferative therapy.**"

In some embodiments, the methods of the preset disclosure may combine the use of the small molecule compounds of any one of **Formulas I** to **VII**, as disclosed herein, with at least one chemotherapeutic drug or agent. More specifically, **"chemotherapeutic drugs or agents"** are drugs used to treat cancer and some proliferative diseases. The treatment that uses these drugs intend to stop the growth of cancer cells or other proliferating cells (malignancy and proliferative disease), either by killing the cells or by stopping them from dividing. **Chemotherapy** may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated. It may be given alone or with other treatments, such as surgery, radiation therapy, or biologic therapy. The mechanism underlying the activity of some chemotherapeutic drugs is based on destructing rapidly dividing cells, as many cancer cells grow and multiply more rapidly than normal cells. As a result of their mode of activity, chemotherapeutic agents also harm cells that rapidly divide under normal circumstances, for example bone marrow cells, digestive tract cells, and hair follicles. Insulting or damaging normal cells result in the common side-effects of chemotherapy: myelosuppression (decreased production of blood cells, hence also immuno-suppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss).

Certain chemotherapy agents have also been used in the treatment of conditions other than cancer and therefore considered as "anti-proliferative", including ankylosing spondylitis, multiple sclerosis, hemangiomas, Crohn's disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, lupus and scleroderma.

Chemotherapeutic drugs affect cell division or DNA synthesis and function and can be generally classified into groups, based on their structure or biological function. Some chemotherapeutic agents are classified as alkylating agents, anti-metabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other anti-tumor agents such as DNA-alkylating agents, anti-tumor antibiotic agents, tubulin stabilizing agents, tubulin destabilizing agents, hormone antagonist agents, protein kinase inhibitors, HMG-CoA inhibitors, CDK inhibitors, cyclin inhibitors, caspase inhibitors, metalloproteinase inhibitors, antisense nucleic acids, triple-helix DNAs, nucleic acids aptamers, and molecularly-modified viral, bacterial or exotoxic agents.

However, several chemotherapeutic drugs may be classified as relating to more than a single group. It is noteworthy that some agents, including monoclonal antibodies and tyrosine kinase inhibitors, which are sometimes referred to as "chemotherapy", do not directly interfere with DNA synthesis or cell division but rather function by targeting specific components that differ between cancer cells and normal cells and are generally referred to as "targeted therapies", "biological therapy" or "immunotherapy" as detailed below.

In some embodiments, the methods of the preset disclosure may combine the use of the small molecule compounds of any one of **Formulas I** to **VII**, as disclosed herein, with at least one targeted therapy. More specifically, **"targeted therapy"** is a type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells or deliver toxic substances directly to cancer cells and kill them. Targeted therapy may have fewer side effects than other types of cancer treatment. Most targeted therapies are either small molecule drugs or monoclonal antibodies.

In some embodiments, the methods of the preset disclosure may combine the use of the small molecule compounds of any one of **Formulas I** to **VII**, as disclosed herein, with at least one drug or agent considered as a biological therapy. More specifically,

"**biological therapy**" is a type of treatment that uses substances made from living organisms to treat disease. These substances may occur naturally in the body or may be made in the laboratory. In cancer, some biological therapies stimulate or suppress the immune system to help the body fight cancer. Other biological therapies attack specific cancer cells, which may help keep them from growing or kill them. They may also lessen certain side effects caused by some cancer treatments. Types of biological therapy include immunotherapy (such as cytokines, cancer treatment vaccines, and some antibodies) and some targeted therapies. Also called biological response modifier therapy, biotherapy, and biological response modifiers (BRM) therapy.

Still further, in some embodiments, the methods of the preset disclosure may combine the use of the small molecule compounds of any one of **Formulas I** to **VII**, as disclosed herein, with at least one chemotherapeutic drug or agent. More specifically, **"Immunotherapy**", is a type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way. Cancer Immunotherapy uses certain components of the immune system to stimulate the immune system to become more efficient in attacking cancer cells by administering vaccines or by administering components of the immune system like cytokines and antibodies. Novel anti-cancer immunotherapies include immune checkpoint inhibitors (e.g., PD1, PDL1, CTLA4 inhibitors) and T cell-based therapy such as Chimeric Antigen T cell Receptor, known as CAR-T.

In some embodiments, the methods of the preset disclosure may combine the use of the small molecule compounds of any one of **Formulas I** to **VII**, as disclosed herein, with at radiation therapy. More specifically, **"radiation therapy"** is a type of cancer treatment that uses beams of intense energy to kill cancer cells. Radiation therapy most often uses X-rays, gamma rays and charged particles like protons or other types of energy also can be used.

Still further, it must be understood that in some embodiments, the methods of the preset disclosure may combine the use of the small molecule compounds of any one of Formulas I to VII, as disclosed herein, with any surgical approaches. More specifically, cancer **" surgery**", is a procedure to remove or repair a part of the body suffering from a tumor, or to find out whether disease is present. Said tumor can be benign or malignant, solid, or liquid.

In yet some further embodiments, the methods of the preset disclosure may combine the use of the small molecule compounds of any one of **Formulas I** to **VII**, as disclosed herein, with **radiosurgery.** More specifically, **"radiosurgery",** is a type of external radiation therapy that uses special equipment to position the patient and precisely give a single large dose of radiation to a tumor. It is used to treat brain tumors and other brain disorders that cannot be treated by regular surgery. It is also being studied in the treatment of other types of cancer. Also called radiation surgery, stereotactic radiosurgery, and stereotaxic radiosurgery.

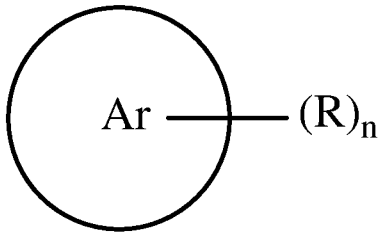
In some embodiments, the methods of the preset disclosure may combine the use of the small molecule compounds of any one of **Formulas I** to **VII**, as disclosed herein, with at hormone therapy. More specifically, "**Hormone therapy**", as used herein, is a treatment that adds, blocks, or removes hormones. Hormones can also cause certain cancers (such as prostate and breast cancer) to grow. In the context of the present invention "hormone therapy" describes a treatment aiming to slow or stop the growth of cancer, synthetic hormones or other drugs may be given to block the body's natural hormones, or surgery is used to remove the gland that makes a certain hormone. Also called endocrine therapy, hormonal therapy, and hormone treatment.

In some further embodiments, the method of the present disclosure is applicable for subjects suffering from at least one proliferative malignant disease, for example, at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

Yet, in some further embodiments, the proliferative malignant disease treated by the methods of the present disclosure may be a metastatic disease originated from a primary and/or secondary proliferative malignant disease, said proliferative malignant disease is at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

In some embodiments, the method disclosed herein may be applicable for a primary proliferative malignant disease that exists in a dormant, inactive state.

In another aspect the present invention provides an inhibitory effective amount of at least one small molecule compound for use in a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject treated with at least one anti-proliferative therapy. In some embodiments, said compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any compositions thereof, and wherein said **Formula I** is:

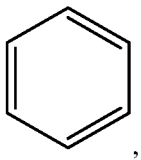


Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of said R may be the same or different.

In some embodiments, Ar of the compound for use by the method of the present disclosure is selected from the group consisting of:

a)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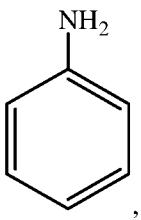

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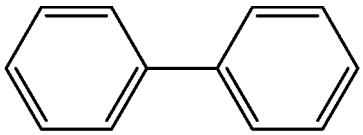

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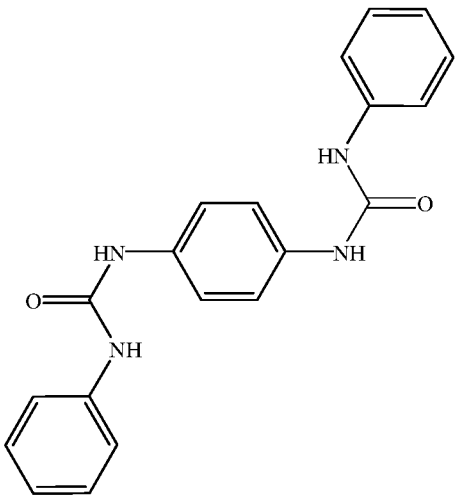
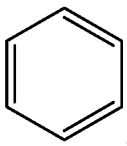


wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)



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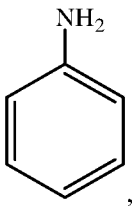
b)



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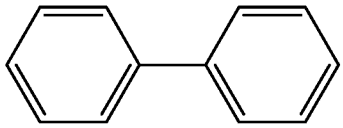

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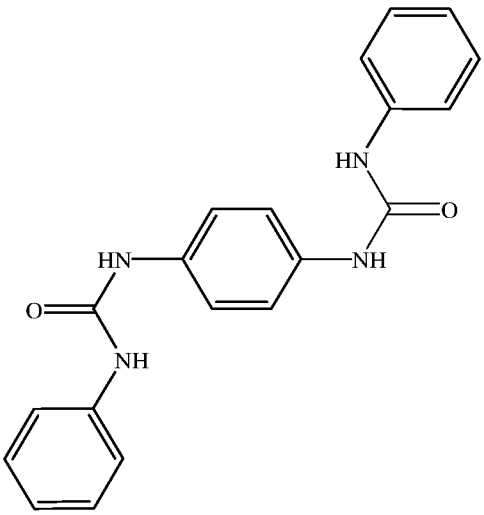
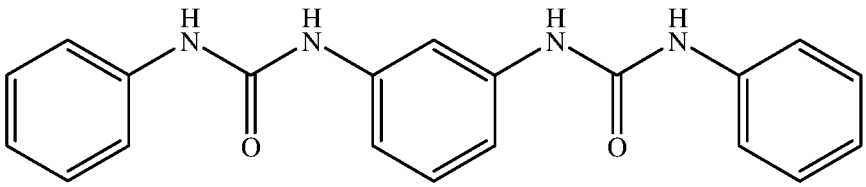


, and

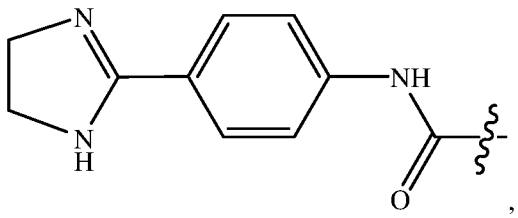
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In some embodiments, R of the compound for use in the present disclosure is selected from the group consisting of:

a)



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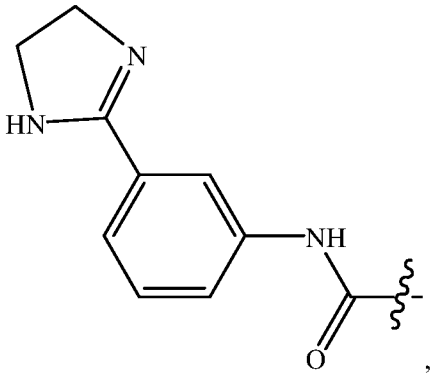
b)



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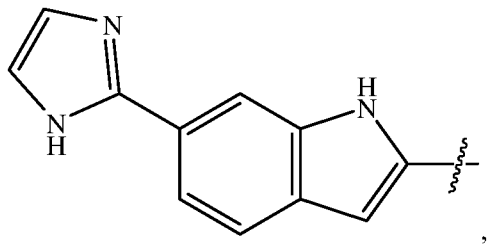
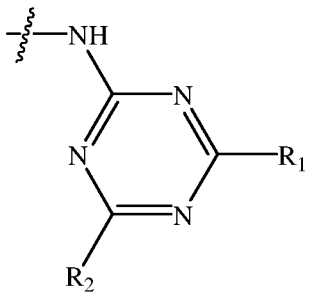
c)



, and

d)

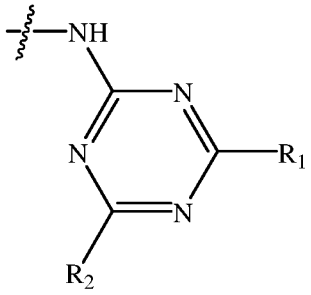


wherein R_1 and R_2 each are independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

and wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

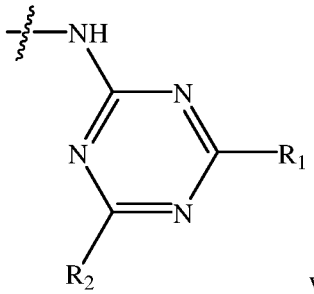
In some embodiments at least one of R is



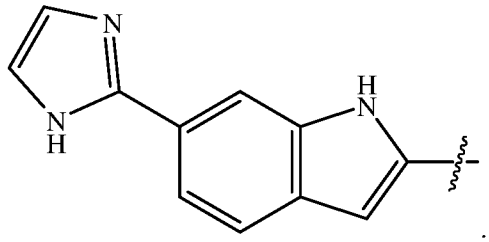
wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$.

In some specific embodiments of the method of the present disclosure, at least one of the R is an imidazole derivative and a triazine derivative.

In some embodiments at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



In some further embodiments, the R of the compound for use in the present disclosure, is an imidazole derivative.

In some specific embodiments of the method of the present disclosure, the at least one of the R is a dihydroimidazole derivative.

In some specific embodiments of the method of the present disclosure, at least one of the R is a dihydroimidazole derivative.

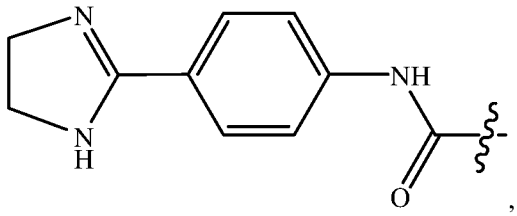
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative which may be the same or different.

In some specific embodiments, the R of the compound for use in the present disclosure, is repeated n times. In some embodiments n is 2, 3, or 4.

In some specific embodiments of the method of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

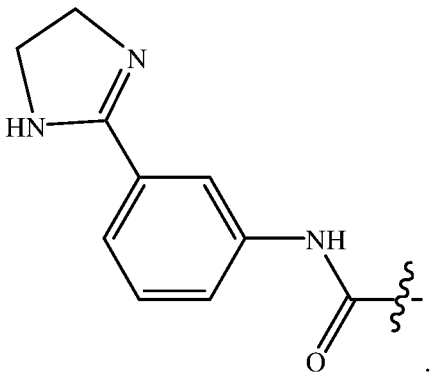
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



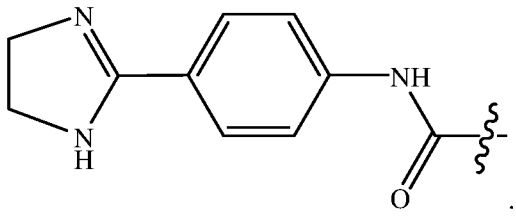
, or

b)



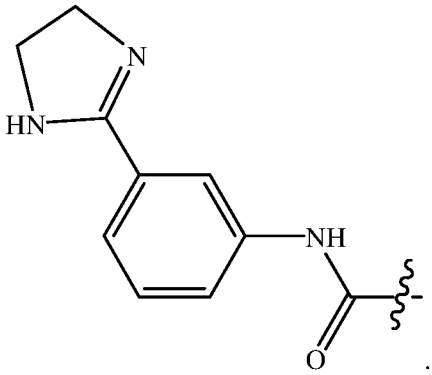
.

In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



.

In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



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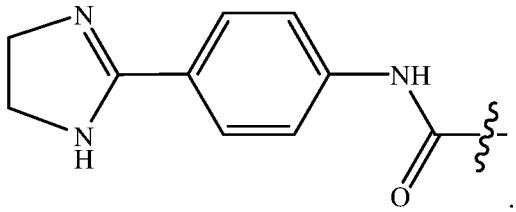
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



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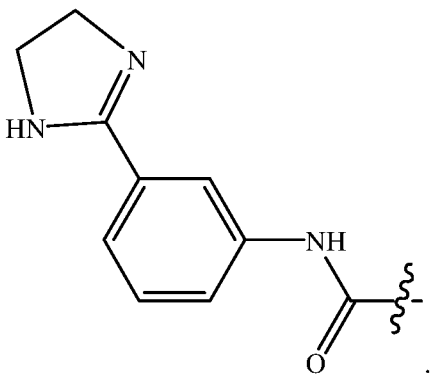
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



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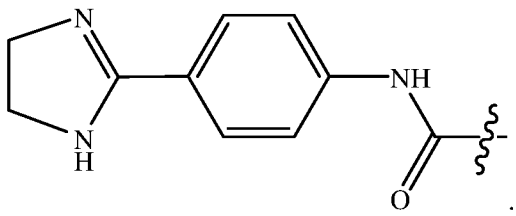
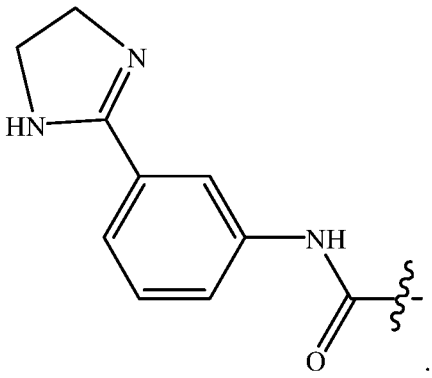
In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative

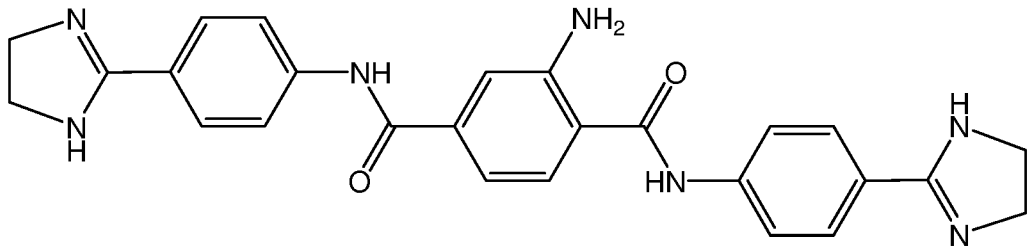


In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



In some embodiments, the present disclosure provides the use of the compound of at least one of **Formulas III**, **IV**, **V**, **VI** and/or **VII**, and any combinations thereof.

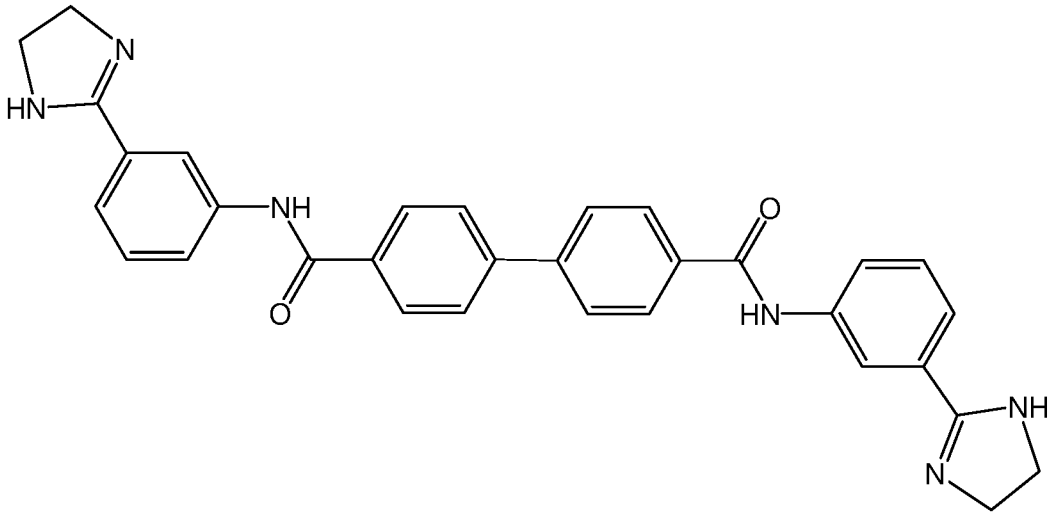
In some embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula III**:



Formula III

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula III**, is also designated by the present disclosure as compound #2.

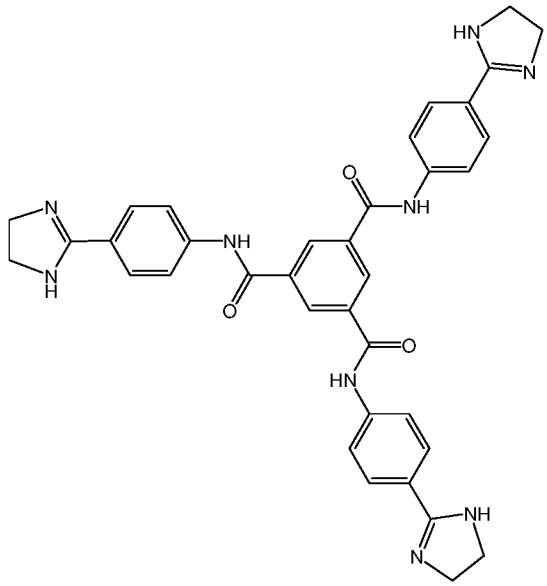
In yet some further embodiments, the at least one small molecule compound of F**ormula I** for use in the methods of the present disclosure may be the compound of **Formula IV**:



Formula IV

a salt thereof, any conjugates thereof. As used herein, this compound of **Formula IV**, is also designated by the present disclosure as compound #1.

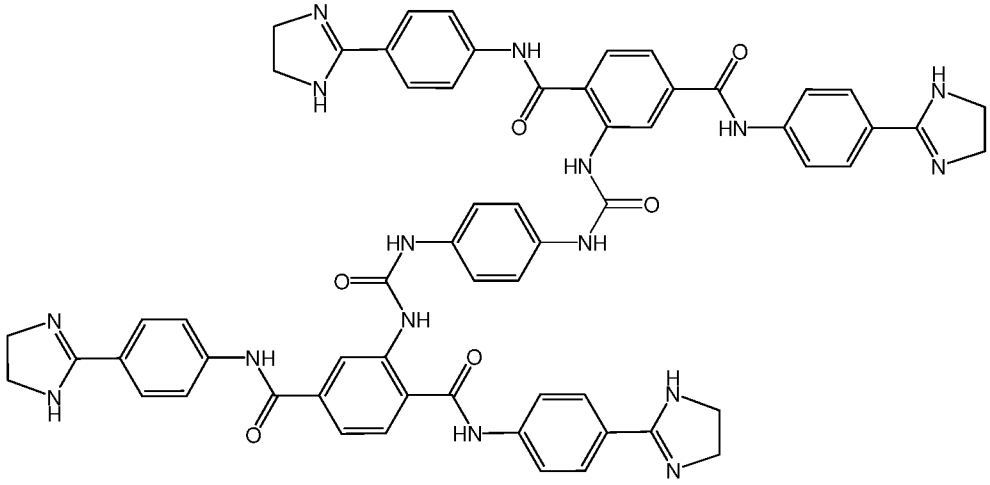
In some further embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula V**:



Formula V

a salt thereof, any conjugates thereof. As used herein, this compound of **Formula V**, is also designated by the preset disclosure as compound #3.

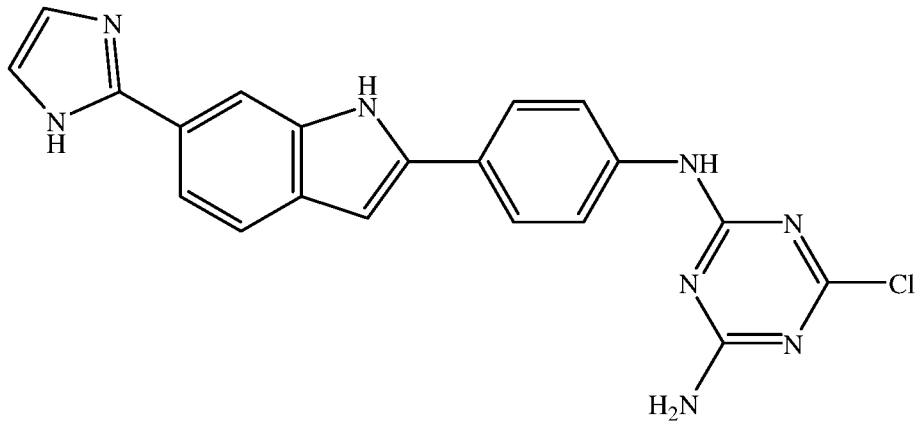
In some further embodiments, the at least one small molecule compound of **Formula I** for use in the methods of the present disclosure may be the compound of **Formula VI**:



Formula VI

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VI**, is also designated by the present disclosure as compound #4.

Still further, in some embodiments, the at least one small molecule compound of Formula I for use in the methods of the present disclosure may be the compound of **Formula VII**:



Formula VII

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VII**, is also designated by the present disclosure as compound #6.

The compounds for use, disclosed in the present disclosure are combined herein for treating subjects treated with anti-proliferative therapy, that may comprise in some embodiments at least one of chemotherapy, radiosurgery, radiation therapy, biological therapy, immune-therapy, hormone therapy, surgery, or any combination thereof.

In some further embodiments, the method of the present disclosure is applicable for use in subjects suffering from at least one proliferative malignant disease, for example, at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, specifically, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

Yet, in some further embodiments, methods of the present disclosure are for use in treating proliferative malignant disease that may be a metastatic disease originated from a primary and/or secondary proliferative malignant disease, said proliferative malignant disease is at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, sarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

In some embodiments, the method disclosed herein may be for use in a primary proliferative malignant disease that exists in a dormant, inactive state.

As discussed herein, the present disclosure provides effective small molecule compounds, specifically those of **Formulas I**, **II**, **III**, IV, **V**, **VI**, **VII**, and uses thereof in cancer therapy, either as a sole therapy or in combination with anti-proliferative compounds as disclosed herein. Thus, the present disclosure offers therapeutic approaches for treating any malignant proliferative disorders. In more specific embodiments, the proliferative disorder may be at least one solid and non-solid tumor.

It should be understood that the present invention is further applicable to any metastatic tissue, organ or cavity of any of the disclosed proliferative disorders. As used herein to describe the present invention, "**proliferative disorder**", "**cancer**", "**tumor**" and "**malignancy**" all relate equivalently to a hyperplasia of a tissue or organ. If the tissue is a part of the lymphatic or immune systems, malignant cells may include non-solid tumors of circulating cells. Malignancies of other tissues or organs may produce solid tumors. In general, the methods, compositions and uses of the present invention may be applicable for a patient suffering from any one of non-solid and solid tumors.

Malignancy, as contemplated in the present invention may be any one of carcinomas, melanomas, lymphomas, leukemia, myeloma and sarcomas. Therefore, in some embodiments any of the methods of the invention (specifically, therapeutic, prognostic and non-therapeutic methods), uses and compositions disclosed herein, may be applicable for any of the malignancies disclosed by the present disclosure.

More specifically, carcinoma as used herein, refers to an invasive malignant tumor consisting of transformed epithelial cells. Alternatively, it refers to a malignant tumor composed of transformed cells of unknown histogenesis, but which possess specific molecular or histological characteristics that are associated with epithelial cells, such as the production of cytokeratins or intercellular bridges.

Melanoma as used herein, is a malignant tumor of melanocytes. Melanocytes are cells that produce the dark pigment, melanin, which is responsible for the color of skin. They predominantly occur in skin but are also found in other parts of the body, including the bowel and the eye. Melanoma can occur in any part of the body that contains melanocytes.

Leukemia refers to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number of abnormal cells in the blood-leukemic or aleukemic (subleukemic).

Sarcoma is a cancer that arises from transformed connective tissue cells. These cells originate from embryonic mesoderm, or middle layer, which forms the bone, cartilage, and fat tissues. This is in contrast to carcinomas, which originate in the epithelium. The epithelium lines the surface of structures throughout the body, and is the origin of cancers in the breast, colon, and pancreas.

Myeloma as mentioned herein is a cancer of plasma cells, a type of white blood cell normally responsible for the production of antibodies. Collections of abnormal cells accumulate in bones, where they cause bone lesions, and in the bone marrow where they interfere with the production of normal blood cells. Most cases of myeloma also feature the production of a paraprotein, an abnormal antibody that can cause kidney

problems and interferes with the production of normal antibodies leading to immunodeficiency. Hypercalcemia (high calcium levels) is often encountered.

Lymphoma is a cancer in the lymphatic cells of the immune system. Typically, lymphomas present as a solid tumor of lymphoid cells. These malignant cells often originate in lymph nodes, presenting as an enlargement of the node (a tumor). It can also affect other organs in which case it is referred to as extranodal lymphoma. Non limiting examples for lymphoma include Hodgkin's disease, non-Hodgkin's lymphomas and Burkitt's lymphoma.

In some embodiments, the compounds of the present disclosure are particularly applicable for breast cancer, specifically, metastatic breast cancer. As used herein, the term "*breast cancer*" refers to a cancer that develops from breast tissue. Development of breast cancer is often associated with a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, or a red scaly patch of skin. Breast cancer classification divides breast cancer into categories according to different schemes, each based on different criteria and serving a different purpose. The major categories are the histopathological type, the grade of the tumor, the stage of the tumor, and the expression of proteins and genes. Classification includes at least one of the following parameters histopathological type, grade, stage (TNM), receptor status, and the presence or absence of certain receptors and markers. Staging of breast cancer may be done by various methods for example using TNM staging which takes into account the size of the tumor (T), whether the cancer has spread to the lymph glands (lymph nodes) (N), and whether the tumor has spread anywhere else in the body (M – for metastases). Receptor status can also be used for classification of breast cancer into several molecular classes. The three most important receptors in the classification being: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Breast cells characterized by being ER+ (cells expressing ER) and low grade are denoted Luminal A. Breast cells characterized by being ER+ and but often high grade are denoted as Luminal B. Triple-negative breast cancers (TNBCs) are regarded as aggressive types of breast cancer and are the product of impaired expression of progesterone and estrogen receptors as well as human growth factor receptor 2. There are four transcriptional subtypes of TNBCs: two basal subtypes, which are grouped as BL1 and BL2, a mesenchymal subtype M, and a luminal androgen receptor subtype. Further, TNBC can be categorized into six different subgroups based on their molecular heterogeneity: immunomodulatory, luminal androgen receptor expression,

mesenchymal stem-like, mesenchymal-like, basal-like, and unstable. TNBC is one of the most aggressive subtypes of cancer that is often associated with poor patient outcomes because of the development of metastases in secondary organisms like in the brain, bone, and lungs. It should be understood that in some embodiments, the compounds of the present disclosure are applicable for any aggressive subtype of TNBC.

Still further, in some embodiments, the compounds of the preset disclosure may be applicable for treating melanoma. Skin cancer is by far the most common of all cancers, with an increasing frequency in the past three decades that includes basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. Although melanoma accounts for merely 1% of all skin cancers, it is responsible for the majority of skin cancer related fatalities. Melanoma is the most aggressive and dangerous forms of skin cancer that develops from the transformed pigment forming cells of the skin, melanocytes. Melanoma patients can be classified into five distinct stages, 0, I, II, III, and IV, as the stage increases the prognosis is worse. Stage 0 is defined as melanoma *in situ* while stage IV melanoma is known as metastatic melanoma. Metastatic melanoma is defined by the dissemination of primary melanoma cells to distant organs including but not limited to the lymph nodes, lungs, liver, brain, and bone. AJCC criteria uses different permutations of the TNM system, to categorize melanoma from early stage to late-stage melanoma. The TNM system is defined as: Tumor thickness with or without ulceration, Nodal involvement, and Metastasis. The three major histological variants of melanoma include superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM) and nodular melanoma (NM). However, other variants such as acral lentiginous melanoma, mucosal melanoma, desmoplastic melanoma and nevoid melanoma have been also described. It should be therefore noted that the compounds of the present disclosure are applicable for any variant of melanoma, particularly metastatic and invasive variants of melanoma.

In yet some further embodiments, the compounds of the present disclosure may be applicable for treating pancreatic cancer, specifically, any malignant, invasive and metastatic PC. Pancreatic cancer (PC), in spite of arising as a thirteenth cancer worldwide, is the fourth most common cause of death due to cancer. The incidence and mortality rates of PC have been increasing year by year worldwide. Pancreatic adenocarcinoma and its variants account for 90% of all pancreatic carcinomas. It should be understood that the compounds of the resent disclosure are applicable for any stage, specifically any advanced stage of PC.

Still further, in some embodiments, the compounds of the present disclosure are specifically applicable for treating lung caner, specifically, any aggressive, invasive and metastatic lung cancer. Lung cancer causes most cancer-related deaths worldwide. Clinical staging of non-small cell lung cancer (NSCLC) is difficult. Although separate diagnostic modalities have high sensitivity and specificity, comparing the clinical stage (cTNM) and pathological stage (pTNM) has an accuracy that is generally low, between 50–60%. In some embodiments, the compounds of the present disclosure may be applicable for locally advanced NSCLC (stage III) and to advanced NSCLC (stage IV).

In yet some further embodiments, the compounds of the present disclosure are applicable for treating Hepatocellular carcinoma. More specifically, s used herein, Hepatocellular carcinoma (HCC), the primary cancer of the liver, is derived from hepatocytes and occurs in more than approximately 80% of cases of liver cancer. HCC development results from the interaction between environmental and genetic factors. Liver cirrhosis, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, excessive alcohol consumption, ingestion of aflatoxin B1, and nonalcoholic steatohepatitis (NASH) are important risk factors for HCC development. It should be understood that the compounds of the resent disclosure are applicable for any stage, specifically any advanced stage of HCC.

In some embodiments, the methods of the present disclosure may be applicable for any solid tumor. In more specific embodiments, the methods disclosed herein may be applicable for any malignancy that may affect any organ or tissue in any body cavity, for example, the peritoneal cavity (e.g., liposarcoma), the pleural cavity (e.g., mesothelioma, invading lung), any tumor in distinct organs, for example, the urinary bladder, ovary carcinomas, and tumors of the brain meninges.

Still further, as discussed above, the methods of the present disclosure are applicable for any metastatic cancer that display reduced or abolished expression and/or activity of KAI1/CD82. Still further, in some embodiments, the methods of the present disclosure are applicable for any metastatic cancer that display enhanced expression of KAI1 as-lncRNA. It should be understood that the methods, compositions and uses of the present disclosure are applicable for any type and/or stage and/or grade of any of the malignant disorders discussed herein or any metastasis thereof. Still further, it must be appreciated that the methods, compositions and uses of the invention may be applicable for invasive as well as non-invasive cancers. When referring to "*non-invasive*" cancer it should be noted as a cancer that do not grow into or invade normal tissues within or beyond the

primary location. When referring to "*invasive cancers*" it should be noted as cancer that invades and grows in normal, healthy adjacent tissues.

Still further, in some embodiments, the methods, compositions and uses of the present disclosure are applicable for any type and/or stage and/or grade of any metastasis, metastatic cancer or status of any of the cancerous conditions disclosed herein.

As used herein the term "*metastatic cancer*" or "*metastatic status*" refers to a cancer that has spread from the place where it first started (primary cancer) to another place in the body. A tumor formed by metastatic cancer cells originated from primary tumors or other metastatic tumors, that spread using the blood and/or lymph systems, is referred to herein as a metastatic tumor or a metastasis.

Further malignancies that may find utility in the present invention can comprise but are not limited to hematological malignancies (including lymphoma, leukemia, myeloproliferative disorders, Acute lymphoblastic leukemia; Acute myeloid leukemia), hypoplastic and aplastic anemia (both virally induced and idiopathic), myelodysplastic syndromes, all types of paraneoplastic syndromes (both immune mediated and idiopathic) and **solid tumors** (including GI tract, colon, lung, liver, breast, prostate, pancreas and Kaposi's sarcoma). The invention may be applicable as well for the treatment or inhibition of **solid tumors** such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extraliepatic bile ducts, ampulla of vater, exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri, corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter, urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva, malignant melanoma of the uvea, retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma, Adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; Anal cancer; Appendix cancer; Astrocytoma, childhood cerebellar or cerebral; Basal cell carcinoma; Bile duct cancer, extrahepatic; Bladder cancer; Bone cancer, Osteosarcoma/Malignant fibrous histiocytoma; Brainstem glioma; Brain tumor; Brain tumor, cerebellar astrocytoma; Brain tumor, cerebral astrocytoma/malignant glioma; Brain tumor, ependymoma; Brain tumor, medulloblastoma; Brain tumor, supratentorial primitive neuroectodermal tumors; Brain tumor, visual pathway and hypothalamic

glioma; Breast cancer; Bronchial adenomas/carcinoids; Burkitt lymphoma; Carcinoid tumor, childhood; Carcinoid tumor, gastrointestinal; Carcinoma of unknown primary; Central nervous system lymphoma, primary; Cerebellar astrocytoma, childhood; Cerebral astrocytoma/Malignant glioma, childhood; Cervical cancer; Childhood cancers; Chronic lymphocytic leukemia; Chronic myelogenous leukemia; Chronic myeloproliferative disorders; Colon Cancer; Cutaneous T-cell lymphoma; Desmoplastic small round cell tumor; Endometrial cancer; Ependymoma; Esophageal cancer; Ewing's sarcoma in the Ewing family of tumors; Extracranial germ cell tumor, Childhood; Extragonadal Germ cell tumor; Extrahepatic bile duct cancer; Eye Cancer, Intraocular melanoma; Eye Cancer, Retinoblastoma; Gallbladder cancer; Gastric (Stomach) cancer; Gastrointestinal Carcinoid Tumor; Gastrointestinal stromal tumor (GIST); Germ cell tumor: extracranial, extragonadal, or ovarian; Gestational trophoblastic tumor; Glioma of the brain stem; Glioma, Childhood Cerebral Astrocytoma; Glioma, Childhood Visual Pathway and Hypothalamic; Gastric carcinoid; Hairy cell leukemia; Head and neck cancer; Heart cancer; Hepatocellular (liver) cancer; Hodgkin lymphoma; Hypopharyngeal cancer; Hypothalamic and visual pathway glioma, childhood; Intraocular Melanoma; Islet Cell Carcinoma (Endocrine Pancreas); Kaposi sarcoma; Kidney cancer (renal cell cancer); Laryngeal Cancer; Leukemias; Leukemia, acute lymphoblastic (also called acute lymphocytic leukemia); Leukemia, acute myeloid (also called acute myelogenous leukemia); Leukemia, chronic lymphocytic (also called chronic lymphocytic leukemia); Leukemia, chronic myelogenous (also called chronic myeloid leukemia); Leukemia, hairy cell; Lip and Oral Cavity Cancer; Liver Cancer (Primary); Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphomas; Lymphoma, AIDS-related; Lymphoma, Burkitt; Lymphoma, cutaneous T-Cell; Lymphoma, Hodgkin; Lymphomas, Non- Hodgkin (an old classification of all lymphomas except Hodgkin's); Lymphoma, Primary Central Nervous System; Marcus Whittle, Deadly Disease; Macroglobulinemia, Waldenstrom; Malignant Fibrous Histiocytoma of Bone/Osteosarcoma; Medulloblastoma, Childhood; Melanoma; Melanoma, Intraocular (Eye); Merkel Cell Carcinoma; Mesothelioma, Adult Malignant; Mesothelioma, Childhood; Metastatic Squamous Neck Cancer with Occult Primary; Mouth Cancer; Multiple Endocrine Neoplasia Syndrome, Childhood; Multiple Myeloma/Plasma Cell Neoplasm; Mycosis Fungoides; Myelodysplastic Syndromes; Myelodysplastic/Myeloproliferative Diseases; Myelogenous Leukemia, Chronic;

Myeloid Leukemia, Adult Acute; Myeloid Leukemia, Childhood Acute; Myeloma, Multiple (Cancer of the Bone-Marrow); Myeloproliferative Disorders, Chronic; Nasal cavity and paranasal sinus cancer; Nasopharyngeal carcinoma; Neuroblastoma; Non-Hodgkin lymphoma; Non-small cell lung cancer; Oral Cancer; Oropharyngeal cancer; Osteosarcoma/malignant fibrous histiocytoma of bone; Ovarian cancer; Ovarian epithelial cancer (Surface epithelial-stromal tumor); Ovarian germ cell tumor; Ovarian low malignant potential tumor; Pancreatic cancer; Pancreatic cancer, islet cell; Paranasal sinus and nasal cavity cancer; Parathyroid cancer; Penile cancer; Pharyngeal cancer; Pheochromocytoma; Pineal astrocytoma; Pineal germinoma; Pineoblastoma and supratentorial primitive neuroectodermal tumors, childhood; Pituitary adenoma; Plasma cell neoplasia/Multiple myeloma; Pleuropulmonary blastoma; Primary central nervous system lymphoma; Prostate cancer; Rectal cancer; Renal cell carcinoma (kidney cancer); Renal pelvis and ureter, transitional cell cancer; Retinoblastoma; Rhabdomyosarcoma, childhood; Salivary gland cancer; Sarcoma, Ewing family of tumors; Sarcoma, Kaposi; Sarcoma, soft tissue; Sarcoma, uterine; Sezary syndrome; Skin cancer (nonmelanoma); Skin cancer (melanoma); Skin carcinoma, Merkel cell; Small cell lung cancer; Small intestine cancer; Soft tissue sarcoma; Squamous cell carcinoma - see Skin cancer (nonmelanoma); Squamous neck cancer with occult primary, metastatic; Stomach cancer; Supratentorial primitive neuroectodermal tumor, childhood; T-Cell lymphoma, cutaneous (Mycosis Fungoides and Sezary syndrome); Testicular cancer; Throat cancer; Thymoma, childhood; Thymoma and Thymic carcinoma; Thyroid cancer; Thyroid cancer, childhood; Transitional cell cancer of the renal pelvis and ureter; Trophoblastic tumor, gestational; Unknown primary site, carcinoma of, adult; Unknown primary site, cancer of, childhood; Ureter and renal pelvis, transitional cell cancer; Urethral cancer; Uterine cancer, endometrial; Uterine sarcoma; Vaginal cancer; Visual pathway and hypothalamic glioma, childhood; Vulvar cancer; Waldenstrom macroglobulinemia and Wilms tumor (kidney cancer).

As discussed herein, the present disclosure provides therapeutic methods for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject. It is to be understood that the terms "treat", "treating", "treatment" or forms thereof, as used herein, mean, ameliorating or delaying the onset of one or more clinical indications of disease activity in a subject having a pathologic disorder. Treatment refers to therapeutic treatment.

Those in need of treatment are subjects suffering from a pathologic disorder. Still further, in some embodiments thereof, the present disclosure further provides a "preventive treatment" (to prevent) or a "prophylactic treatment" acting in a protective manner, to defend against or prevent something, especially a condition or disease. The term “treatment and/or prevention” as used herein, refers to the complete range of therapeutically positive effects of administrating to a subject including inhibition, reduction of, alleviation of, and relief from, pathologic disorder involved with at least one malignant proliferative condition/process and any associated condition, illness, symptoms, undesired side effects or related disorders. More specifically, treatment or prevention of relapse or recurrence of the disease, includes the prevention or postponement of development of the disease, prevention or postponement of development of symptoms and/or a reduction in the severity of such symptoms that will or are expected to develop. These further include ameliorating existing symptoms, preventing- additional symptoms and ameliorating or preventing the underlying metabolic causes of symptoms. It should be appreciated that the terms "inhibition", "moderation", “reduction”, "decrease" or "attenuation" as referred to herein, relate to the retardation, restraining or reduction of a process by any one of about 1% to 99.9%, specifically, about 1% to about 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, about 45% to 50%, about 50% to 55%, about 55% to 60%, about 60% to 65%, about 65% to 70%, about 75% to 80%, about 80% to 85% about 85% to 90%, about 90% to 95%, about 95% to 99%, or about 99% to 99.9%, 100% or more.

With regards to the above, it is to be understood that, where provided, percentage values such as, for example, 10%, 50%, 120%, 500%, etc., are interchangeable with "fold change" values, i.e., 0.1, 0.5, 1.2, 5, etc., respectively.

The term "amelioration" as referred to herein, relates to a decrease in the symptoms, and improvement in a subject's condition brought about by the compositions and methods according to the invention, wherein said improvement may be manifested in the forms of inhibition of pathologic processes associated with the disorders described herein, a significant reduction in their magnitude, or an improvement in a diseased subject physiological state.

The term "inhibit" and all variations of this term is intended to encompass the restriction or prohibition of the progress and exacerbation of pathologic symptoms or a pathologic process progress, said pathologic process symptoms or process are associated with.

The term "eliminate" relates to the substantial eradication or removal of the pathologic symptoms and possibly pathologic etiology, optionally, according to the methods of the invention described herein.

The terms "delay", "delaying the onset", "retard" and all variations thereof are intended to encompass the slowing of the progress and/or exacerbation of a disorder associated with the at least one malignant proliferative condition/process and their symptoms, slowing their progress, further exacerbation or development, so as to appear later than in the absence of the treatment according to the invention.

As indicated above, the methods and compositions provided by the present invention may be used for the treatment of a “pathological disorder”, i.e., pathologic disorder or condition involved with at least one malignant proliferative condition/process, which refers to a condition, in which there is a disturbance of normal functioning, any abnormal condition of the body or mind that causes discomfort, dysfunction, or distress to the person affected or those in contact with that person. It should be noted that the terms "disease", "disorder", "condition" and "illness", are equally used herein.

It should be appreciated that any of the methods, uses and compositions described by the invention may be applicable for treating and/or ameliorating any of the disorders disclosed herein or any condition associated therewith. It is understood that the interchangeably used terms "associated", “linked” and "related", when referring to pathologies herein, mean diseases, disorders, conditions, or any pathologies which at least one of: share causalities, co-exist at a higher than coincidental frequency, or where at least one disease, disorder condition or pathology causes the second disease, disorder, condition or pathology. More specifically, as used herein, “disease”, “disorder”, “condition”, “pathology” and the like, as they relate to a subject's health, are used interchangeably and have meanings ascribed to each and all of such terms.

In some embodiments present invention relates to the treatment of subjects or subject suffering or patients, in need thereof. By **“patient”** or **"subject suffering" “subject in need”** it is meant any organism who may be affected by any kind of "malignancy", "cancer", or "proliferative disease", including mammals and specifically humans. By “**mammalian subject**” is meant any mammal for which the proposed therapy is desired,

including , livestock, equine, canine, rodents and feline subjects, primates and most specifically humans.

The present disclosure relates to the use of particular small molecules derived from the compound of Formula I, and any derivatives thereof. A "**small molecule**" as used herein, is an organic molecule that is less than about 2 kilodaltons (kDa) in mass. In some embodiments, the small molecule is less than about 1.5 kDa, or less than about 1 kDa. In some embodiments, the small molecule is less than about 800 daltons (Da), 600 Da, 500 Da, 400 Da, 300 Da, 200 Da, or 100 Da. Often, a small molecule has a mass of at least 50 Da. In some embodiments, a small molecule is non-polymeric. In some embodiments, a small molecule is not an amino acid. In some embodiments, a small molecule is not a nucleotide. In some embodiments, a small molecule is not a saccharide. In some embodiments, a small molecule contains multiple carbon-carbon bonds and can comprise one or more heteroatoms and/ or one or more functional groups important for structural interaction with proteins (e.g., hydrogen bonding), e.g., an amine, carbonyl, hydroxyl, or carboxyl group, and in some embodiments at least two functional groups. Small molecules often comprise one or more cyclic carbon or heterocyclic structures and/or aromatic or polyaromatic structures, optionally substituted with one or more of the above functional groups.

Still further, the methods disclosed herein involve the use of an effective amount of the small molecule compounds, specifically, the small molecule compounds of **Formulas I-VII**, or any compositions thereof, for therapy. The **"effective treatment amount"** is determined by the severity of the disease in conjunction with the preventive or therapeutic objectives, the route of administration and the patient's general condition (age, sex, weight and other considerations known to the attending physician). More specifically, effective amount as used herein is any amount of the disclosed compounds effective to achieve at least one of inhibit metastatic process, inhibit and/or reduce cell motility and/or invasiveness in a subject, and/or increase the expression of the metastasis suppressor KAI1/CD82.

In yet some further embodiments, an effective amount of the disclosed small molecule compounds provided to a subject may range between about 0.01gr to about 10gr per day/ per kg of body weight. In more specific embodiments, about 0.01gr, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.11. 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.2, 0.21, 0.22, 0.23, 0.24, 0.5, 0.26, 0.27, 0.28, 0.29, 0.3, 0.31, 0.32, 0.33, 0.34, 0.35,

0.36, 0.37, 0.38, 0.39, 0.4, 0.41, 0.42, 0.43, 0.44, 0.45, 0.46, 0.47, 0.48, 0.49, 0.5 gr/kg/day or more, to about 1gr per day/per kg. In yet some further embodiments, an effective amount may range between about 1mg/kg/day or less, to about 500mg/kg/day or more, specifically, 5mg/kg/day or less, to about 100mg/kg/day or more, of any of the disclosed compounds or any combinations and compositions thereof. More specifically, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55. 60, 6, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150 mg/kg/day.

The pharmaceutical compositions of the invention can be administered and dosed by the methods of the invention, in accordance with good medical practice, systemically, for example by parenteral, e.g., intrathymic, into the bone marrow, peritoneal or intraperitoneal, specifically administered to any peritoneal cavity, and any direct administration to any cavity or organ, specifically, the pleural cavity (mesothelioma, invading lung) the urinary bladder and to the brain. It should be noted however that the invention may further encompass any additional administration modes. In other examples, the pharmaceutical composition can be introduced to a site by any suitable route including subcutaneous, transcutaneous, topical, intramuscular, intraarticular, subconjunctival, or mucosal, intravenous, e.g., oral, intranasal, intraocular administration, or intra-tumor as well.

Still further, local administration to the area in need of treatment may be achieved by, for example, by local infusion during surgery, or using any permanent or temporary infusion device, topical application, direct injection into the specific organ, etc. More specifically, the compounds and compositions disclosed herein, that are also used in any of the methods of the invention, described in connection with other aspects of the present disclosure, may be adapted for administration by parenteral, intraperitoneal, transdermal, oral (including buccal or sublingual), rectal, topical (including buccal or sublingual), vaginal, intranasal and any other appropriate routes. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). In some optional embodiment, the small molecule compounds of the present invention as well as any formulations thereof may be administered directly to the central nervous system (CNS). Examples of direct administration into the CNS include intrathecal administration, and direct administration into the brain, such as intra-cerebral, intra-ventricular, intra-cerebroventricular, intra-cranial or subdural routes of administration. Such routes of

administration may be particularly beneficial for diseases involving metastasis, that may in some embodiments affect the central nervous system (e.g., malignant tumors of any neuronal or brain tissue).

In some embodiments the small molecule compounds of any one of **Formulas I** to **VII**, provided by the present disclosure can be formulated as neutral or salt forms. **The term "Pharmaceutically acceptable salts"** include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc. In general terms, under compositions herein is meant predominantly pharmaceutical compositions, meaning that such compositions would comprise a therapeutically effective amount of at least one active agent, i.e., a small molecule compound of any one of **Formulas I** to **VII**, provided by the present disclosure, and optionally, at least one pharmaceutically acceptable carrier. The term **"pharmaceutically acceptable"** means approved by a regulatory agency or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

As indicated above, the present disclosure further encompasses any compositions and formulation of any of the disclosed compounds. In yet some further embodiments, the composition of the invention may optionally further comprise at least one of pharmaceutically acceptable carrier/s, excipient/s, additive/s diluent/s and adjuvant/s.

More specifically, pharmaceutical compositions used to treat subjects in need thereof according to the invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general formulations are prepared by uniformly and intimately bringing into association the active ingredients, specifically, the small molecule compounds of the invention with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product. The compositions may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may

further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol, methanesulfonic acid and/or dextran. The suspension may also contain stabilizers. The pharmaceutical compositions of the present invention also include, but are not limited to, emulsions and liposome-containing formulations, or formulations comprising any other nan- or micro-particles or any matrix comprising the at least one of the small molecule compounds disclosed herein.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may also include other agents conventional in the art having regard to the type of formulation in question.

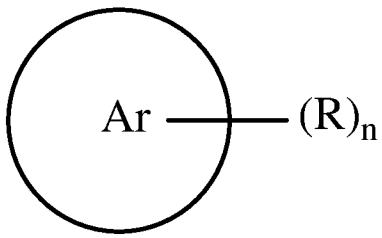
As indicated above, pharmaceutical preparations are compositions that include one or more small molecule compounds present in a pharmaceutically acceptable vehicle. "Pharmaceutically acceptable vehicles" may be vehicles approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in any organism, specifically any vertebrate organism, for example, any mammal such as human. The term "vehicle" refers to a diluent, adjuvant, excipient, or carrier with which a compound of the invention is formulated for administration to a mammal. Such pharmaceutical vehicles can be lipids, e.g. liposomes, e.g. liposome dendrimers; liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like, saline; gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used. Pharmaceutical compositions may be formulated into preparations in solid, semisolid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. As such, administration of the small molecule compounds/s of the invention can be achieved in any of the various ways disclosed by the invention.

Of particular relevance are formulations of compositions of the invention adapted for use as a **"nano- or micro-particles"**. Nanoscale drug delivery systems using liposomes and nanoparticles are emerging technologies for the rational drug delivery, which offers improved pharmacokinetic properties, controlled and sustained release of drugs and, more importantly, lower systemic toxicity. A particularly desired solution allows for

externally triggered release of encapsulated compounds. Externally controlled release can be accomplished if drug delivery **"vehicles",** such as liposomes or polyelectrolyte multilayer capsules, incorporate nanoparticle (NP) actuators.

As indicated in the following Examples, the compounds of **Formulas I**, **II**, **III**, **IV**, **V**, **VI** and **VII**, were targeted, depending on the cells, at the KAI1 as-lncRNA, and therefore, in addition to interaction with this RNA molecule, these small molecule compounds were further evaluated as modulators, and specifically inhibitors of the activity of KAI1 as-lncRNA, specifically, in suppressing the expression and activity of KAI1.

Thus, in yet another aspect the present invention provides a method for modulating the activity of at least one antisense long non-coding RNA of the metastasis suppressor gene KAI1/cluster of differentiation 82 (CD82) (KAI1 as-lncRNA, suppressor of KAI1 in breast cancer (SKAIBC)), in a cell. In some embodiments the method comprising the step of contacting said cell with a modulatory effective amount of at least one small molecule compound of **Formula II**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or with any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any composition thereof, wherein said **Formula II** is:



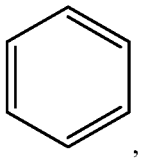
Formula II

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is a dihydroimidazole derivative;

wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10, wherein when n>1, any one of said R may be the same or different, and wherein said KAI1 as-lncRNA has a length of about 700 to about 1000 nucleotides and is encoded upstream of the KAI1/CD82 gene transcription start site (TSS) in an antisense orientation, specifically, the major TSS.

In some embodiments, Ar of the compound used by the method of the present disclosure is selected from the group consisting of:

a)



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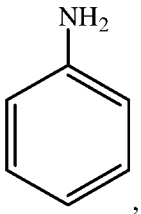
b)



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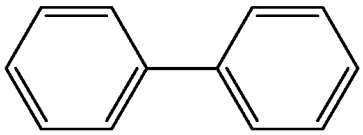
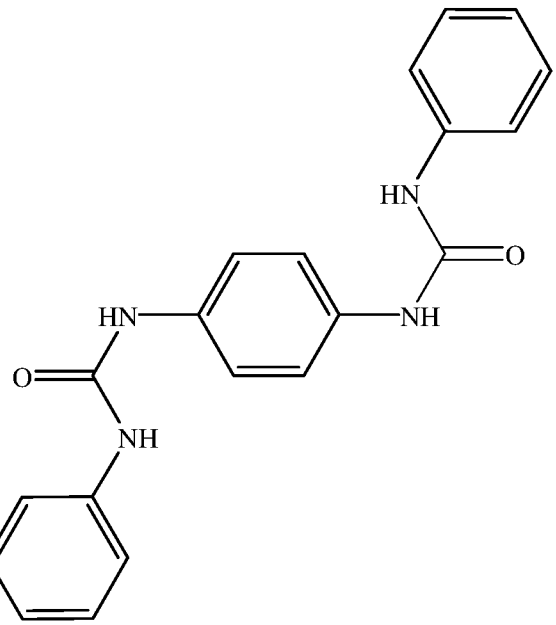
c)



, and

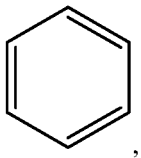
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R, and wherein each of said Ar may optionally be further substituted.

In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)



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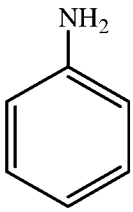
b)



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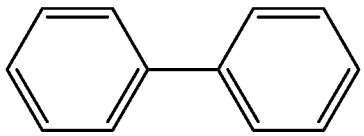
c)



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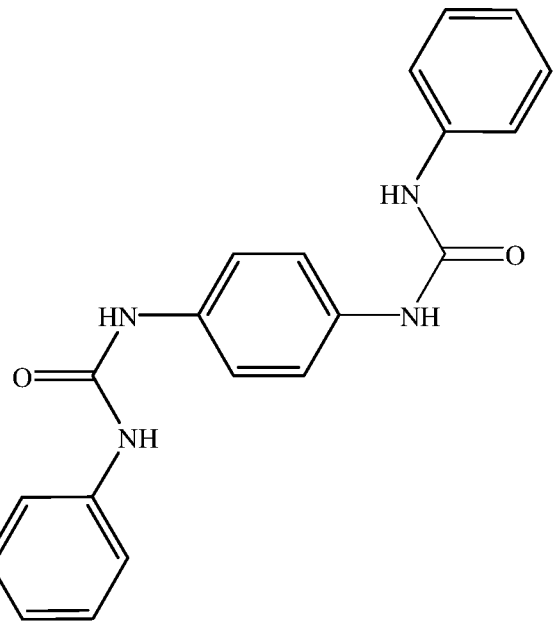
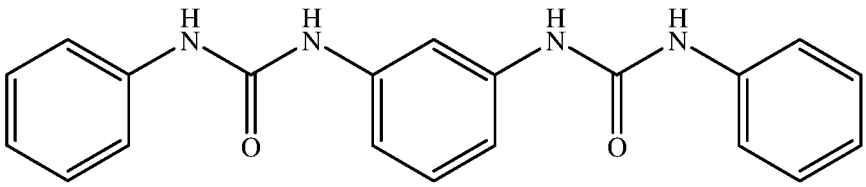
d)



, and

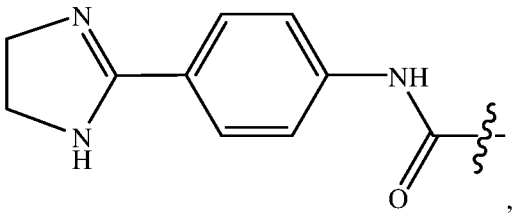
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

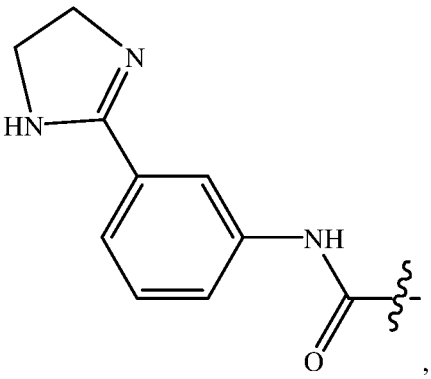
In further embodiment R of the compound used by the method of the present disclosure is selected from the group consisting of:

a)



, and

b)



,

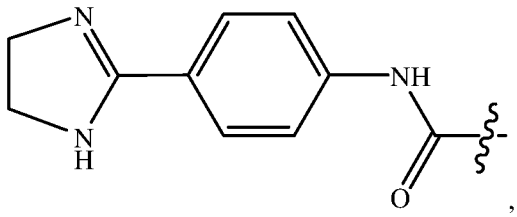
wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

In some specific embodiments of the method of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

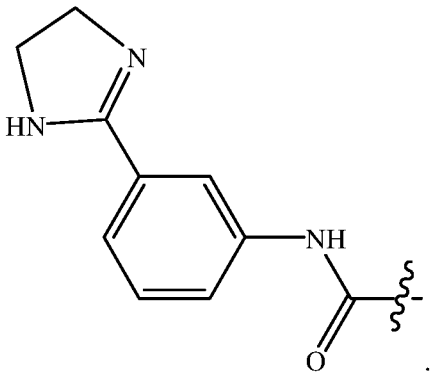
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



, or

b)



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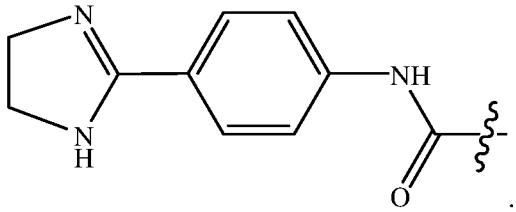
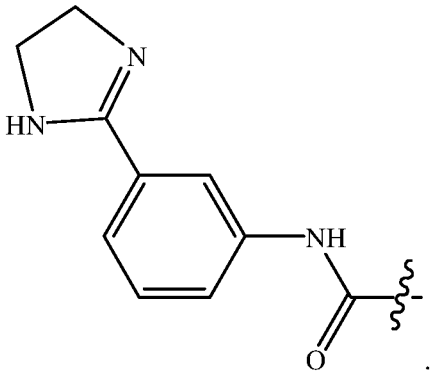
In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



.

In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



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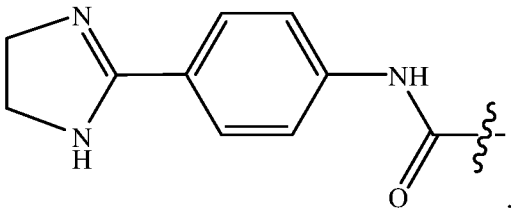
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



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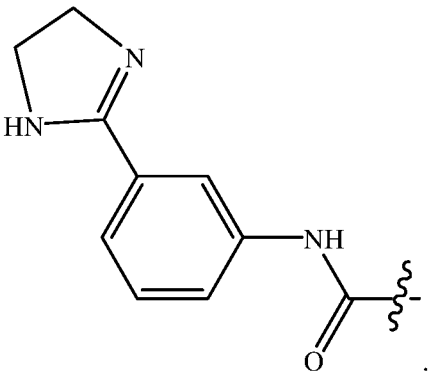
In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



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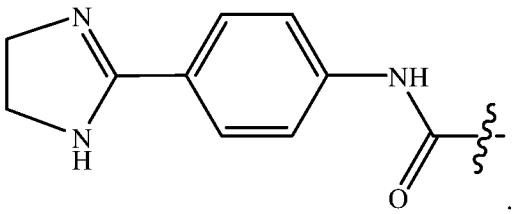
In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



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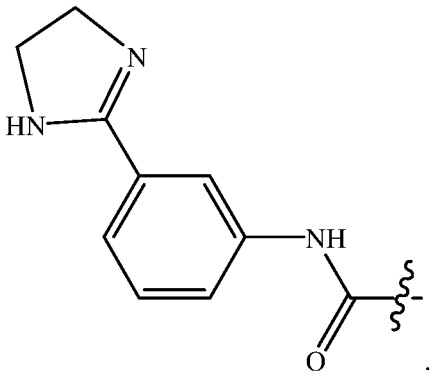
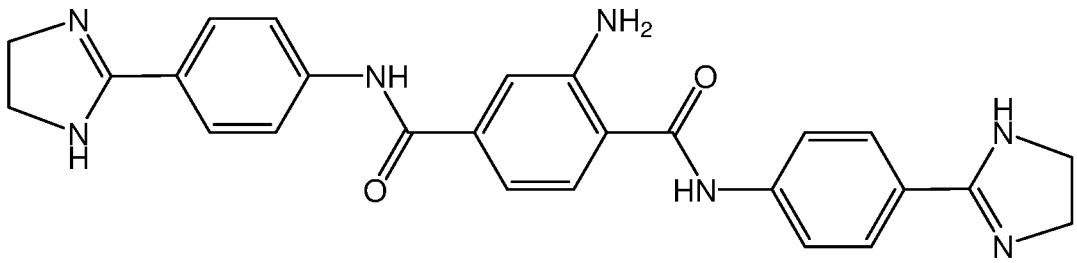
In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



In some more embodiments of the method disclosed herein, R of the compound used by the methods may be repeated n times, wherein n is 2, 3, or 4.

In some embodiments of the method disclosed in the present invention, the compound used in the method are selected from at least one of:

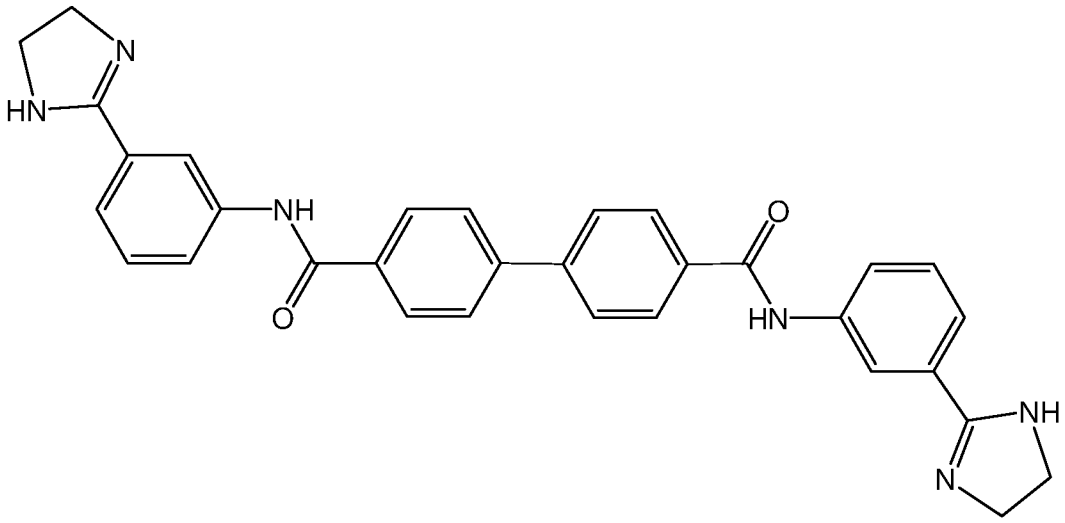
(a)



Formula III

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula III**, is also designated as to as compound #2);

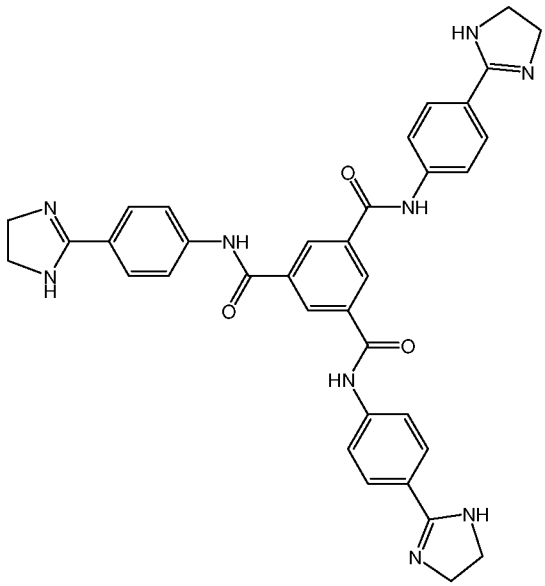
(b)



Formula IV

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula IV**, is also designated as to as compound #1);

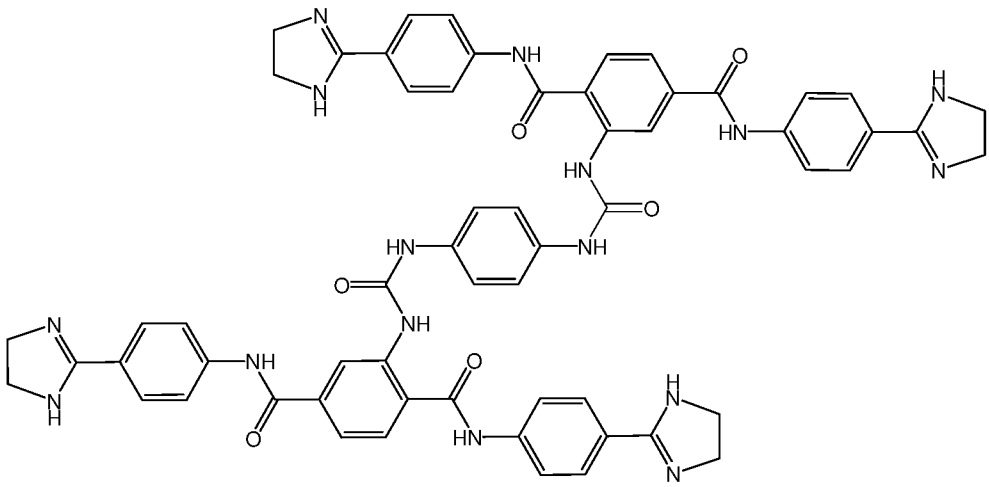
(c)



Formula V

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula V**, is also designated as to as compound #3); and

(d)

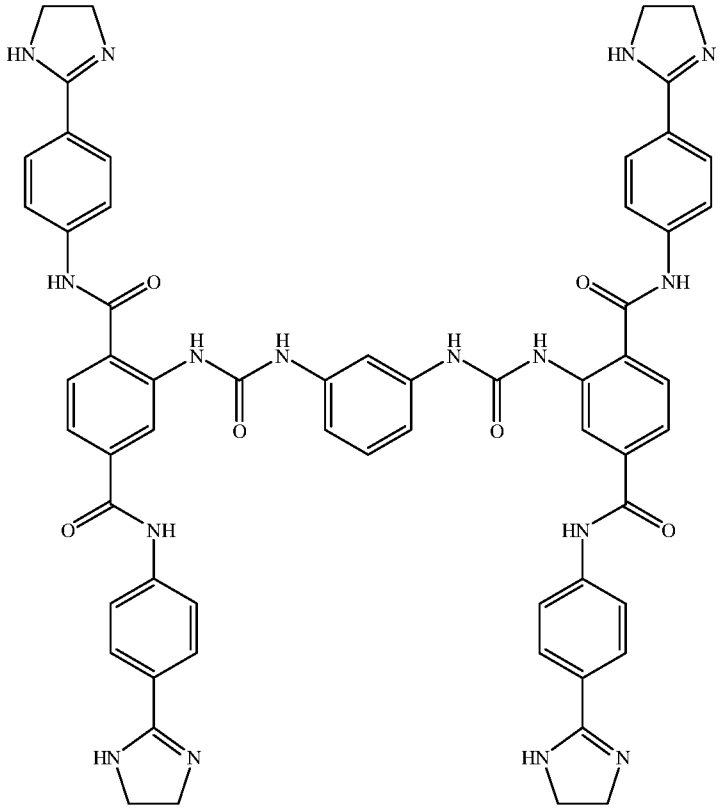


Formula VI

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VI**, is also designated as to as compound #4).

In some embodiments, the compound of **Formula VIII**, that is in some embodiments an isomer of the compound of **Formula VI** (compound #4) may be also used.

In some embodiments, the compound of **Formula VIII** is:



Formula VIII

a salt thereof, or any conjugates thereof. As indicated herein, this compound of **Formula VIII**, is also designated as to as compound #5.

In some embodiments, this compound is also indicated herein as 2-[[3-[[2,5-bis[[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]carbamoyl]phenyl]carbamoylamino]phenyl]carbamoylamino]-1-N,4-N-bis[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]benzene-1,4-dicarboxamide.

CAS # 5300-65-2; Formula: $C_{60}H_{54}N_{16}O_6$; Mw: 1095.1700 gr/mol.

As shown by Example 1 (Figs. 1 and 2), the compounds of **Formulas II**, **III**, **IV**, **V** and **VI**, used by the present disclosure bind and are directed at the long non-coding RNA of KAI1. As used herein, the term **"long non-coding RNA"** or "lncRNA" or "long ncRNA" is functionally defined as non-protein coding RNA transcript that is longer than approximately 200 nucleotides and therefore should be distinguished from small regulatory RNAs such as microRNAs (miRNAs), short interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), and other short

RNAs. It has been recently recognized that lncRNAs are exquisitely regulated, are restricted to specific cell types and frequently have evolutionarily conserved function, secondary structure and regions of micro homology. It is now recognized that lncRNAs may interact with proteins to modulate protein function, regulate protein-protein interactions or direct localization within cellular compartments, and as such may play a role in the control of mRNA stability, splicing and translation. In some embodiments, as being located upstream to the KAI1/CD82 gene, the KAI1 as-lncRNA of the invention may regulate, at least one of the transcription, stability, splicing and translation of the KAI1 gene.

As used herein, an "antisense long non-coding RNA" is a long non-coding RNA whose transcription occurs in the antisense orientation as defined herein below.

More specifically, in some embodiments, the lncRNA of the invention may be located upstream of the KAI1/CD82 gene transcription start site (TSS). The term "transcription" as known in the art refers to the first step of gene expression, in which a particular DNA segment is copied into RNA, for example messenger RNA (mRNA), by the RNA polymerase enzyme. During transcription, a DNA sequence is read by an RNA polymerase, which produces a complementary, antiparallel RNA strand. Transcription proceeds in the following general steps: first an RNA polymerase, together with one or more transcription factors (TFs), binds to promoter DNA. RNA polymerase then creates a transcription bubble, which separates the two strands of the DNA helix. Next the RNA polymerase adds RNA nucleotides (which are complementary to the nucleotides of one DNA strand) and then RNA sugar-phosphate backbone forms with assistance from RNA polymerase to form an RNA strand. Hydrogen bonds of the RNA–DNA helix then break, freeing the newly synthesized RNA strand. The RNA may be further processed by for example polyadenylation, capping, and splicing.

The stretch of DNA transcribed into an RNA molecule is termed "***sense***" strand when encoding at least one protein. If the gene encodes a protein, the template for transcription is termed "antisense" strand (namely the complementary DNA molecule) and transcription produces mRNA identical to the sense strand that serves as a template for protein synthesis by translation. Alternatively, the transcribed gene may encode for example non-coding RNA such as microRNA (miRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), and the like.

Therefore, the term **"antisense orientation"** as used herein refers to the 3' to 5' directionality on the coding DNA strand (sense strand). The coding DNA strand is identical to the messenger RNA (mRNA) and is used to encode the expected protein; for example, ATG in the sense DNA may correspond to an AUG codon in the mRNA, encoding the amino acid methionine.

As indicated above, the KAI1 as-lncRNA of the invention is located upstream of the KAI TSS. The core promoter is the minimal region of DNA required for the RNA polymerase to assemble with the general transcription factors and form the pre-initiation complex for transcription. The core promoter contains the **transcription start site (TSS)**, which is defined as the most 3' nucleotide of the RNA encoding strand, which is transcribed into mRNA by the RNA Polymerase, i.e. the exact location where transcription starts.

As noted above, the lncRNA of the invention may be located upstream of the KAI1/CD82 gene, and therefore may play a role in the regulation of KAI1/CD82 gene expression, function and stability.

KAI1, as used herein refers to the human KAI1 metastasis suppressor gene encoding for a 267 amino acid plasma membrane glycoprotein, which has four transmembrane domains and one large and one small extracellular domain. Plasma membrane expression of KAI1 is downregulated during the progression of several cancers to a metastatic state, including prostate, lung, and pancreatic cancers. KAI1 protein is a member of the transmembrane four superfamily (TM4SF). Members of the TM4SF are cell membrane proteins that contain four hydrophobic, presumably transmembrane, domains and one large extracellular, hydrophilic domain that often contains potential N-linked glycosylation sites. KAI1 (CD82) contains three potential N-linked glycosylation sites and is thus a glycoprotein. KAI1 is identical to the previously characterized antigens R2, IA4, C33 and 4F9 and is designated CD82 by the clusters of differentiation (CD) nomenclature. In some specific embodiments, the KAI1 protein as used herein refers to the human KAI1 protein. More specifically, this protein may comprise the amino acid sequence as disclosed by GenBank: AAC50133.1, specifically, the amino acid sequence as denoted by SEQ ID NO. 3. In yet some further embodiments, the human KAI1 protein is encoded by the nucleic acid sequence as disclosed by GenBank: U20770.1, specifically as denoted by SEQ ID NO. 2.

The KAI1 as-lncRNA of the invention is located upstream of the KAI1 gene. The term used herein "**upstream**" and "**downstream**" both refer to a relative position in DNA or RNA. Each strand of DNA or RNA has a 5' end and a 3' end, so named for the carbon position on the deoxyribose (or ribose) ring. By convention, upstream and downstream relate to the 5' to 3' direction in which RNA transcription takes place. Upstream is toward the 5' end of the DNA or RNA molecule and downstream is toward the 3' end. When considering double-stranded DNA, upstream is toward the 5' end of the protein coding strand for the gene in question and downstream is toward the 3' end. Due to the anti-parallel nature of DNA, this means the 3' end of the mRNA template strand is upstream of the gene and the 5' end is downstream.

As used herein, the term "**5'**" refers to the part of the strand that is closer to the 5' end or **5' terminus**, i.e., to the extremity of the DNA or RNA strand that has a phosphate group attached to the fifth carbon in the sugar-ring of the deoxyribose or ribose at its terminus. Furthermore, the term *"3'"* refers to the part of the strand that is closer to the 3' end or **3' terminus**, i.e., to the extremity of the DNA or RNA strand that has a hydroxyl group linked to the 3rd carbon in the sugar-ring of the deoxyribose or ribose at its terminus.

In addition, in order to define the position of a nucleotide on a DNA coding strand, the terms "minus" (also represented by the "-" symbol) or "plus" (also represented by the "+" symbol) are employed. The term "minus" corresponds to a position which is upstream to the TSS (considered as the position "one") and the term "plus" corresponds to a position which is downstream to the TSS. As indicated above, the KAI1 as-lncRNA, specifically, the 5' terminus thereof may be located in a position of between about 10 to 1000 bp upstream or the KAI1/CD82 gene TSS, specifically, about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000 or more base pairs upstream to KAI1/CD82 gene TSS. In yet some further embodiments, the 5' terminus of the KAI1 as-lncRNA in accordance with the invention may be located at position of between about 250 to 500bp upstream of the KAI1 TSS, specifically, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495, 500bp or more upstream of the KAI1 TSS. In yet some further specific embodiments, the KAI1 as-lncRNA in accordance with the

invention may be located at position of between about 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390 or more bp upstream of the KAI1 TSS. In some particular and non-limiting embodiments, the 5' terminus of the KAI1 as-lncRNA referred to by the invention may be located 386 bp upstream of the KAI1 TSS.

Thus, in some specific embodiments, the 5' terminus of the KAI1 as-lncRNA is located at position -386 of the KAI1 gene transcription start site (TSS). In yet some further specific embodiments, the KAI1 as-lncRNA is located in an antisense orientation. Therefore, as used herein, the "**position -386 of the KAI1 gene transcription start site (TSS)**" corresponds to the 386th nucleotide in the upstream direction (i.e., toward the 5' end) on the DNA coding strand from the TSS of the KAI1 gene.

Still further, according to some embodiments, the KAI1 as-lncRNA of the invention has a length of between about 200 to 1000 or more nucleotides, specifically, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000 or more nucleotides. More specifically, the KAI1 as-lncRNA of the invention has a length of between about 700 or less to 800 or more nucleotides, specifically, 700, 705, 710, 715, 720, 725, 730, 735, 740, 745, 750, 755, 760, 765, 770, 775, 780, 785, 790, 795, 800 or more nucleotides. In yet some further specific embodiments the KAI1 as-lncRNA of the invention has a length of 780 or less to about 800 or more nucleotides, specifically, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800 or more nucleotides. In certain embodiments, the KAI1 as-lncRNA is about 792 nucleotides long, specifically, the KAI1 as-lncRNA is 792 nucleotides long.

In yet some further specific embodiments, the small molecule compounds of **Formulas II, III, IV, V, VI** and **VII**, of the invention modulate the human KAI1 as-lncRNA that comprises a nucleic acid sequence as denoted by SEQ ID NO: 1, or any fragments, homologs or variants thereof.

In some embodiments, the small molecule compounds of **Formulas II**, **III**, **IV**, **V**, **VI** and **VII**, of the invention may reduce the activity of KAI1 as-lncRNA (also referred to herein as SKAI1BC), thereby modulating the expression of the KAI1/CD82 gene. In embodiments, the modulator/s of the invention may modulate the actual activity of SKAI1BC (e.g., via binding and thus blocking its active site/s).

As noted above, the invention provides small molecule compounds of **Formulas II**, **III**, **IV**, **V**, and **VI** directed at KAI1 as-lncRNA that may inhibit KAI1 as-lncRNA activity.

More specifically, the terms "inhibition", "moderation", "reduction" or "attenuation" as referred to herein, relate to the retardation, restraining or reduction of the KAI1 as-lncRNA levels and/or activity by the small molecules of the invention by any one of about 1% to 99.9%, specifically, about 1% to about 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, about 45% to 50%, about 50% to 55%, about 55% to 60%, about 60% to 65%, about 65% to 70%, about 75% to 80%, about 80% to 85% about 85% to 90%, about 90% to 95%, about 95% to 99%, or about 99% to 99.9% or more, specifically, 100%. It should be appreciated that 10%, 50%, 120%, 500%, etc., are interchangeable with "fold change" values, i.e., 0.1, 0.5, 1.2, 5, etc., respectively. 10%, 50%, 120%, 500%, etc., are interchangeable with "fold change" values, i.e., 0.1, 0.5, 1.2, 5, etc., respectively. Therefore, the term inhibition refers to a decrease of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 folds or more.

A further important aspect of the invention relates to small molecule compounds of **Formulas II**, **III**, **IV**, **V**, and **VI** that as disclosed by the present Examples, bind KAI1as-lncRNA, and further provides uses thereof as modulators, and specifically, as inhibitors of at least one antisense long non-coding RNA of the metastasis suppressor gene KAI1/cluster of differentiation 82 (CD82) (KAI1as-lncRNA). In yet some further embodiments, the small molecules of the invention bind KAI1 as-lncRNA that in certain embodiments may be the human KAI1 as-lncRNA, also referred to herein as suppressor of KAI1 in breast cancer (SKAIBC).

In some particular embodiments, the invention provides modulator/s that may lead, either directly or indirectly to reduction in the activity of the KAI1 as-lncRNA transcript, thereby increasing the expression of the KAI1/CD82 gene.

In some embodiments, the small molecule compounds of **Formulas II**, **III**, **IV**, **V**, **VI** and **VII** disclosed herein, may reduce the activity of the KAI1 as-lncRNA or the SKAI1BC.

Without being bound by any theory, the KAI1 as lncRNA may bind in the nuclei its complementary DNA sequences in the region of KAI1 promoter/enhancer and in that way inhibits KAI1 mRNA synthesis. Alternatively, or additionally, this lncRNA may bind protein/s which constitute part of the chromatin complex in this region (the KAI1

bi-directional promoter/enhancer). Such proteins may include transcription factor/s unique for KAI1 gene or for a group of genes.

In some embodiments, the KAI1 as lncRNA "activity" as referred to herein may include the inhibition of KAI1 synthesis (transcription), by blocking at least one of, the KAI1 promoter and/or enhancer, by inhibiting binding, recognition or activity of required transcription factors or alternatively, by disturbing or reducing the stability of the KAI1 gene product, for example, by any of the stability or degradation processes disclosed herein above.

Thus, in some embodiments, a compound that would bind the KAI1 as-lncRNA may distract it from inhibiting the transcription of KAI1.

More specifically, in some particular embodiments, the invention provides small molecule compounds of **Formulas II**, **III**, **IV**, **V**, **VI** and **VII**, that may lead, either directly or indirectly to reduction in activity of the KAI1 as-lncRNA transcript, thereby increasing the expression of the KAI1/CD82 gene.

In some particular embodiments, the invention provides small molecule compounds of **Formulas II**, **III**, **IV**, **V**, **VI** and **VII** that may lead, either directly or indirectly to reduction in the activity of the KAI1 as-lncRNA transcript, thereby increasing the expression of the KAI1/CD82 gene.

In some embodiments of the method of the present disclosure the selected small molecule compounds of **Formula II**, reduces the activity, thereby increasing the expression of the KAI1/CD82 gene.

In some embodiments the method of the present disclosure, results in the inhibition of at least one metastatic property of the cell.

In some further embodiments the method disclosed herein, results in the inhibition of at least one metastatic property of the cell, wherein said metastatic property is at least one of cell invasiveness, cell motility, cell migration and cell adhesion.

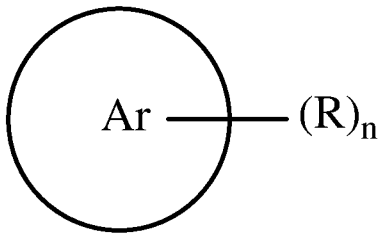
In yet in some further embodiments the disclosed method, results in the inhibition of at least one metastatic property of the cell, wherein said cell is a mammalian malignant cancer cell.

In some embodiments the method of the present disclosure is used to reduce at least one metastatic property of a mammalian malignant cancer cell. In some embodiments, wherein said mammalian malignant cancer cell is of a primary and/or secondary origin of at least one of breast tissue, bone tissue, bladder tissue, kidney tissue, hepatic tissue,

pancreatic tissue, colorectal tissue, gastric tissue, lung tissue, skin tissue, ovarian tissue, prostate tissue, thyroid tissue, cervical tissue, endometrium tissue, laryngeal tissue and hematopoietic tissue.

In some embodiments said mammalian malignant cancer cell is in a subject suffering from a malignant proliferative disease.

In another aspect of the present disclosure at least one small molecule compound of Formula II, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or any vehicle, matrix, nano-, micro-particles thereof, for use in a method for modulating the activity of at least one antisense long non-coding RNA of the metastasis suppressor gene KAI1/cluster of differentiation 82 (CD82) (KAI1 as-lncRNA, suppressor of KAI1 in breast cancer (SKAIBC)), in a cell, wherein said **Formula II** is:



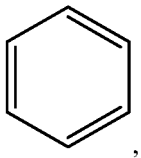
Formula II

wherein in some embodiments Ar is an aromatic or heteroaromatic moiety; wherein R is a dihydroimidazole derivative;

wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; wherein when n>1, any one of said R may be the same or different, and wherein said KAI1 as-lncRNA has a length of about 700 to about 1000 nucleotides and is encoded upstream of the KAI1/CD82 gene transcription start site (TSS) in an antisense orientation, and wherein said KAI1 as-lncRNA has a length of about 700 to about 1000 nucleotides and is encoded upstream of the KAI1/CD82 gene transcription start site (TSS) in an antisense orientation.

In some embodiments, Ar of the compound for use in the present disclosure is selected from the group consisting of:

a)



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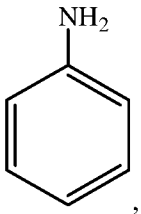
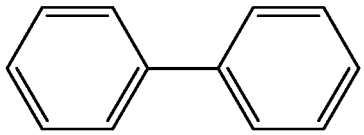
b)



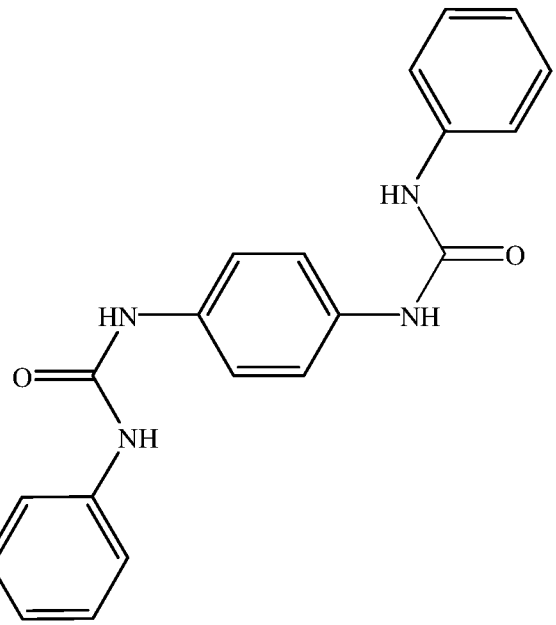
,

c)



, and

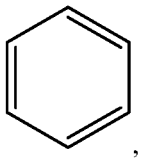
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R, and wherein each of said Ar may optionally be further substituted.

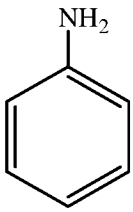
In some embodiments of the method of the present disclosure, Ar of the used compound is selected from the group consisting of:

a)



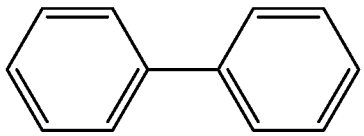
,

b)



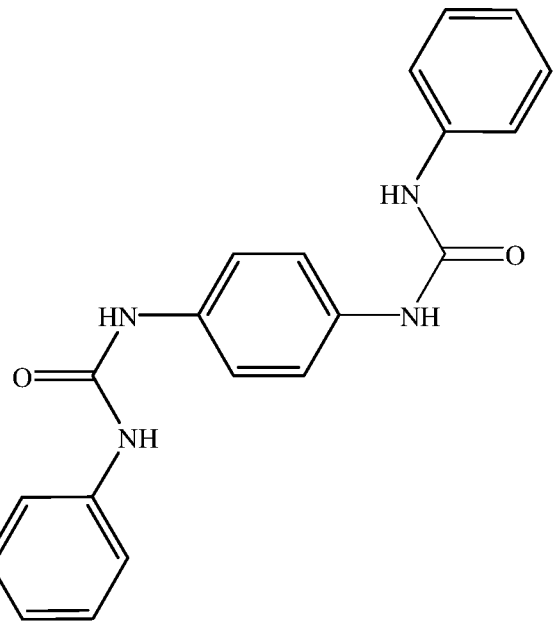
,

c)



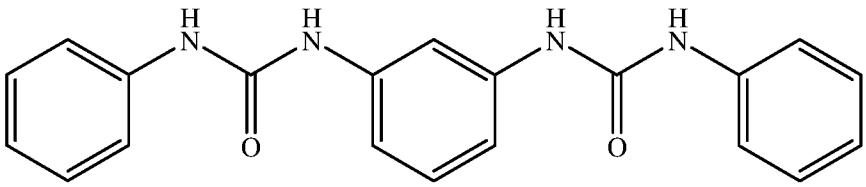
,

d)



, and

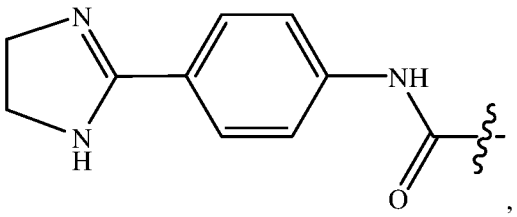
e)



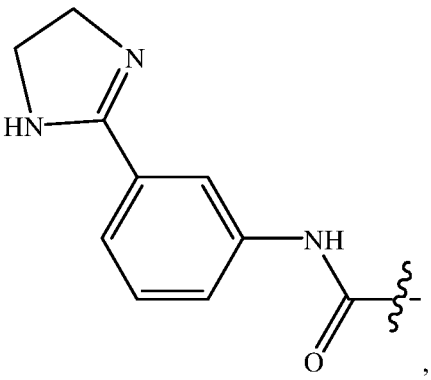
wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In further embodiment R of the compound used by the method of the present disclosure is selected from the group consisting of:

a)



b)



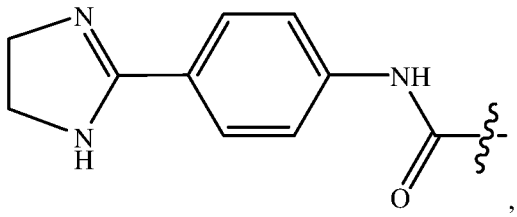
and wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

In some specific embodiments of the method of the present disclosure, n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

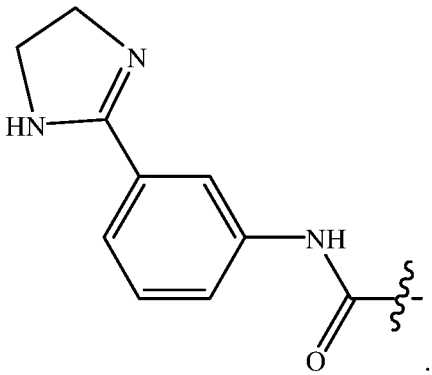
In some specific embodiments of the method of the present disclosure, R is one or more dihydroimidazole derivative selected from

a)



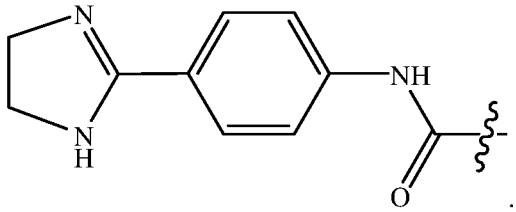
, or

b)



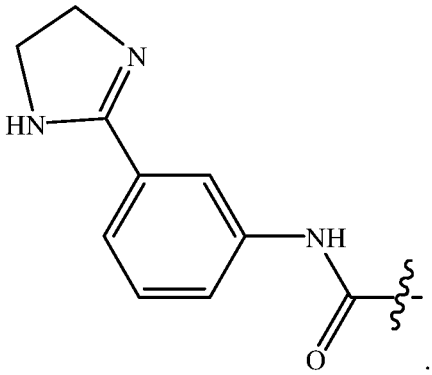
.

In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



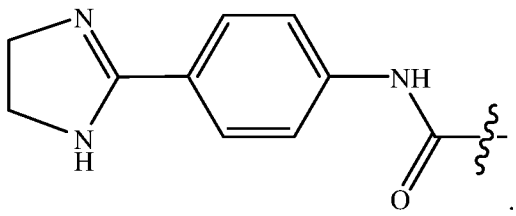
.

In some specific embodiments of the method of the present disclosure, n may be 2 and each of R is the dihydroimidazole derivative



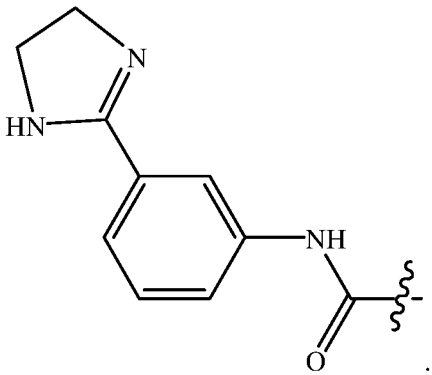
.

In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



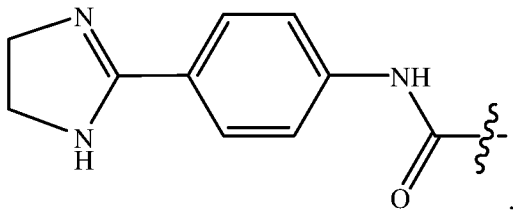
.

In some specific embodiments of the method of the present disclosure, n may be 3 and each of R is the dihydroimidazole derivative



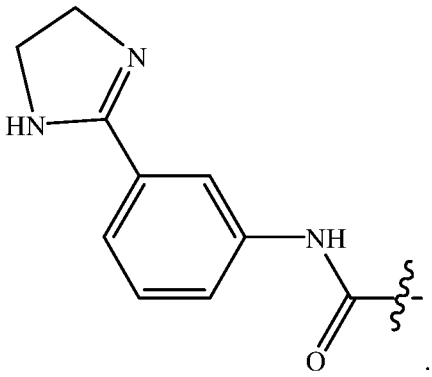
.

In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



.

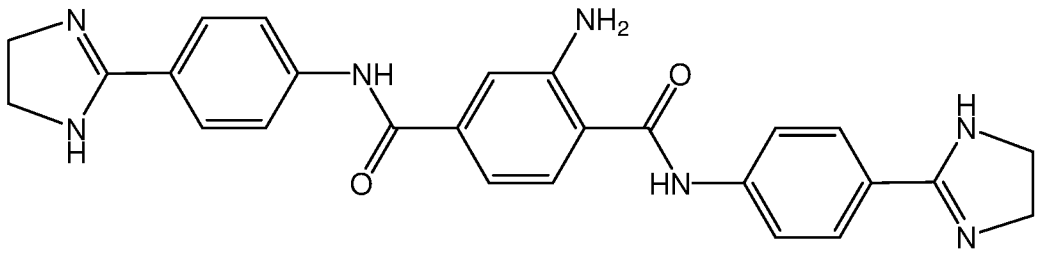
In some specific embodiments of the method of the present disclosure, n may be 4 and each of R is the dihydroimidazole derivative



In some more embodiments of the compounds for use disclosed herein, R of the compound used by the methods may be repeated n times, wherein n is 2, 3, or 4.

In some embodiments of the method disclosed in the present invention, the compound used herein are selected from at least one of:

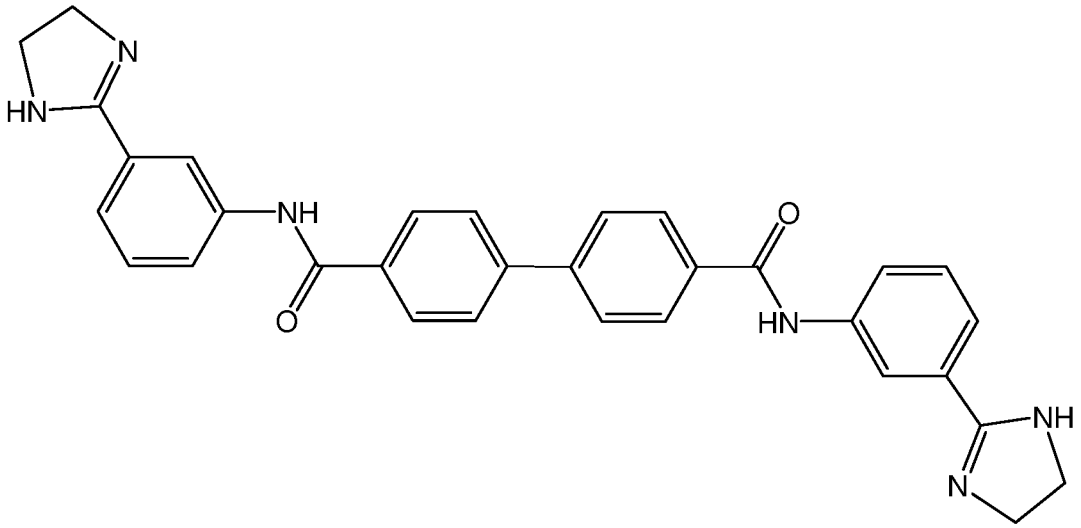
(a)



Formula III

a salt thereof, or any conjugates thereof. As used herein, this compound of **Formula III**, is also designated as to as compound #2);

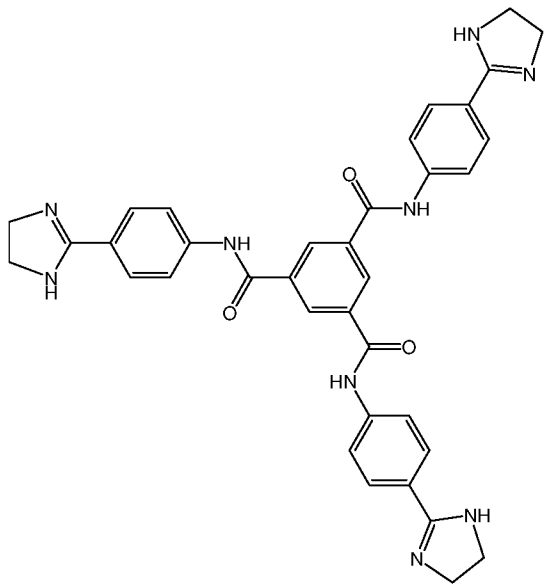
(b)



Formula IV

a salt thereof, any conjugates thereof. As used herein, this compound of **Formula IV**, is also designated as to as compound #1);

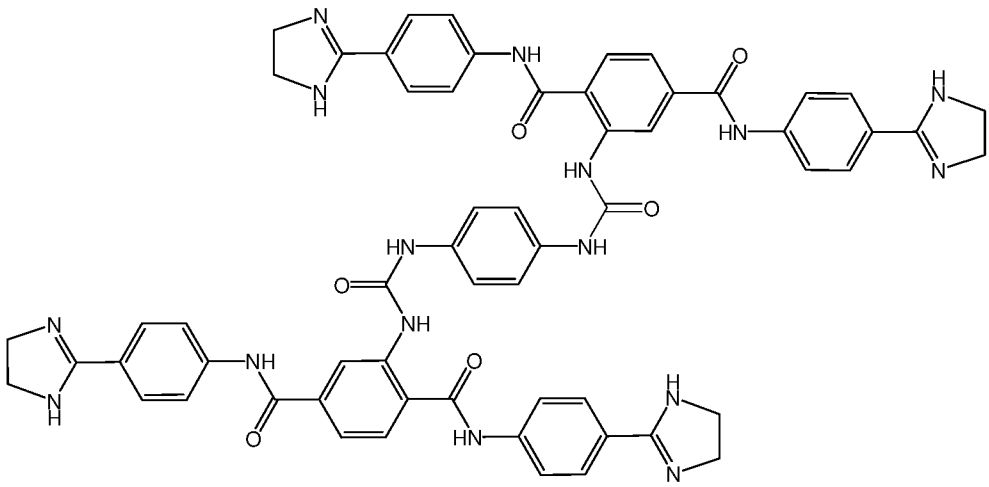
(c)



Formula V

a salt thereof, any conjugates thereof. As used herein, this compound of **Formula V**, is also designated as to as compound #3); and

(d)



Formula VI

any salt thereof, or any conjugates thereof. As used herein, this compound of **Formula VI**, is also designated as to as compound #4).

In some embodiments the method of the present disclosure the selected small molecule compound of **Formula II**, is for use in reducing the activity of the KAI1 as-lncRNA transcript, thereby increasing the expression of the KAI1/CD82 gene.

In some embodiments the small molecule compounds of **Formulas II**, **III**, **IV**, **V**, **VI** and **VII** for use in accordance with the present disclosure, results in the inhibition of at least two metastatic property of said cell. In some specific embodiments these metastatic properties may include, but are not limited to, cell invasiveness and cell migration.

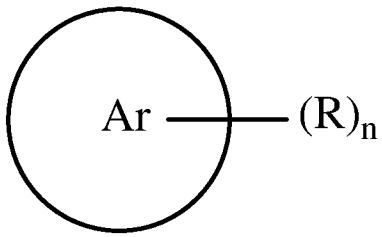
In some further embodiments, the small molecule compounds of **Formulas II**, **III**, **IV**, **V**, **VI** and **VII** for use in accordance with the present disclosure, may result also in the inhibition of the metastatic properties of cell motility and reduced cell adhesion.

Yet in some further embodiments, the small molecule compounds of **Formulas II**, **III**, **IV**, **V**, **VI** and **VII** for use in accordance with the present disclosure are applicable in methods resulting in the inhibition of at least two metastatic properties of said cell, wherein said cell is a mammalian malignant cancer cell.

In some embodiments, the small molecule compounds of **Formulas II**, **III**, **IV**, **V**, **VI** and **VII** for use in accordance with the present disclosure are applicable for reducing at least one metastatic property of a mammalian malignant cancer cell, wherein said mammalian malignant cancer cell is of a primary and/or secondary origin of at least one

of breast tissue, bladder tissue, kidney tissue, hepatic tissue, pancreatic tissue, colorectal tissue, gastric tissue, lung tissue, skin tissue, ovarian tissue, prostate tissue, thyroid tissue, cervical tissue, endometrium tissue, laryngeal tissue and hematopoietic tissue.
In some embodiments said mammalian malignant cancer cell is in a subject suffering from a malignant proliferative disease.

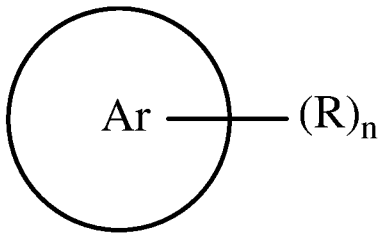
In a further aspect the present invention provides a compound of general **Formula I**



Formula I,

a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or with any vehicle, matrix, nano-, micro-particles thereof,
wherein Ar is an aromatic or heteroaromatic moiety;
wherein R is an imidazole derivative and/or triazine derivative;
wherein each of said Ar and R may optionally be independently further substituted;
wherein n is an integer from 1 to 10; and
wherein when n>1, any one of the R may be the same or different,
provided that said compound of **Formula I** is not any one of the compounds of Formulas IV, III, V, VI, VIII and VII disclosed herein.

In yet a further aspect the present invention provides a compound of general **Formula II**



Formula II,

a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or with any vehicle, matrix, nano-, micro-particles thereof,

wherein Ar is an aromatic or heteroaromatic moiety;

wherein R is a dihydroimidazole derivative;

wherein each of said Ar and R may optionally be independently further substituted;

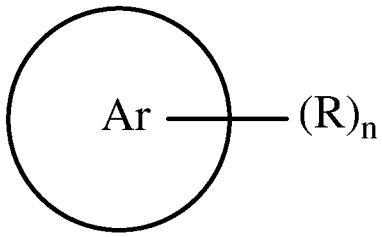
wherein n is an integer from 1 to 10; and

wherein when n>1, any one of the R may be the same or different,

provided that said compound of **Formula II** is not any one of the compounds of Formulas IV, III, V, VI and VIII disclosed herein.

Yet, in a further aspect, the present invention provides a composition comprising at least one compound of the present disclosure, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof. The compositions of the present disclosure may optionally further comprise at least one pharmaceutically acceptable carrier/s, excipient/s, auxiliaries, and/or diluent/s.

Another aspect of the present invention relates to at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or with any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any composition thereof, wherein said **Formula I** is:

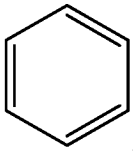


Formula I

wherein Ar is an aromatic or heteroaromatic moiety; wherein R is an imidazole derivative and/or triazine derivative; wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of the R may be the same or different, provided that said at least one small molecule compound of **Formula I** is not any one of compounds #1, #2, #3, #4, #5 and #6, also disclosed herein as compounds of **Formulas IV**, **III**, **V**, **VI**, **VIII** and **VII**, respectively.

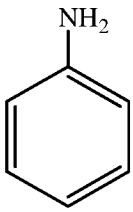
In some embodiments the Ar of the compound of **Formula I**, may be selected from the group consisting of:

a)



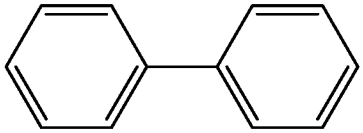
,

b)



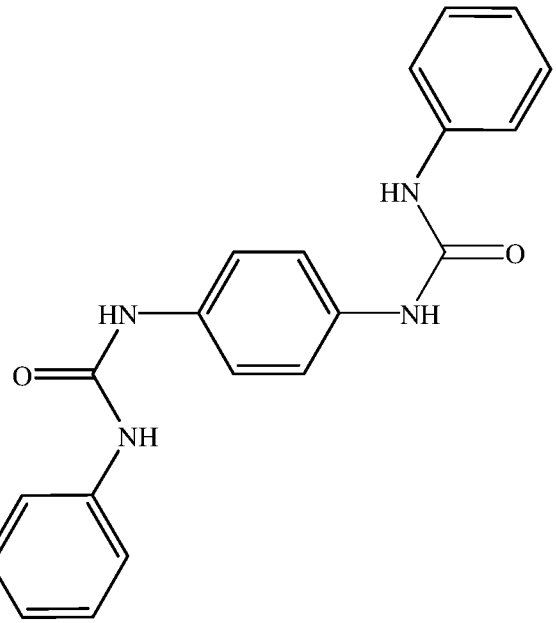
,

c)



, and

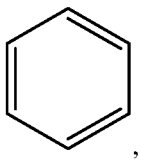
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

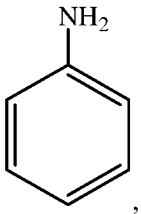
In some embodiments the Ar of the compound of **Formula I** is selected from the group consisting of:

a)



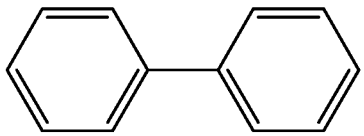
,

b)



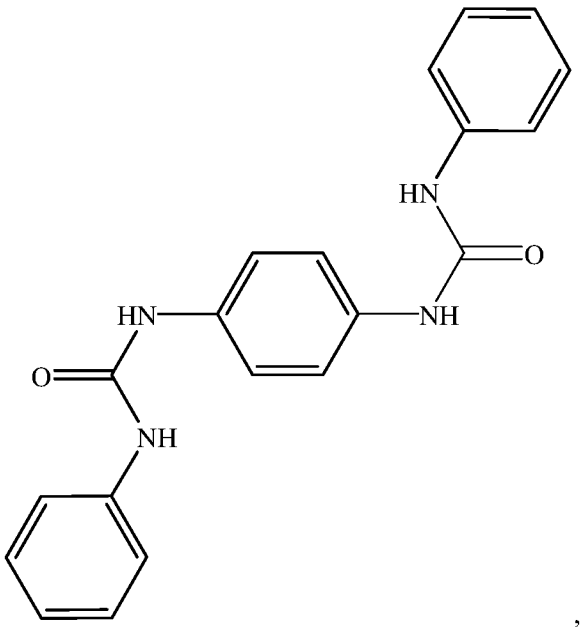
,

c)



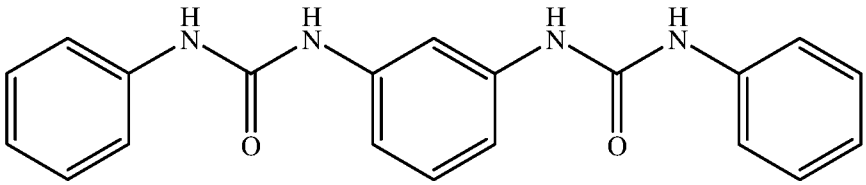
,

d)



, and

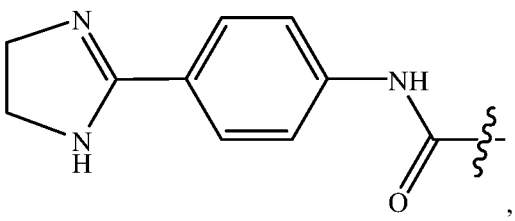
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

In yet some further embodiments the R of the compound of **Formula I**, may be selected from the group consisting of:

a)



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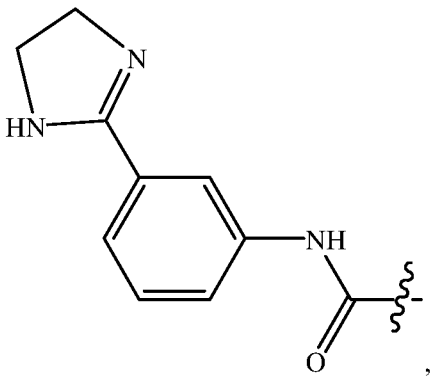
b)



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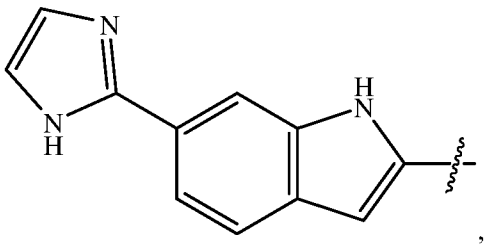
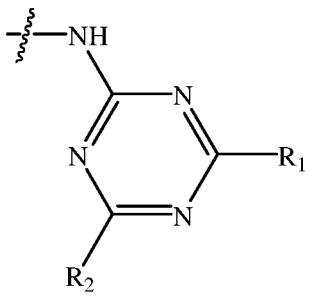
c)



, and

d)

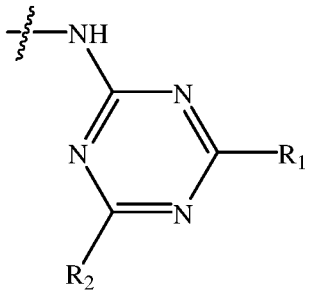


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, -NH_2, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

and wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

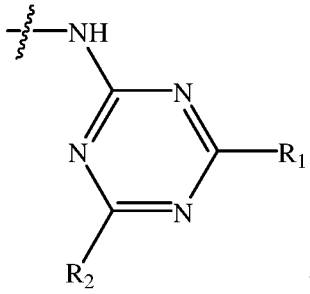
In some embodiments at least one of R is



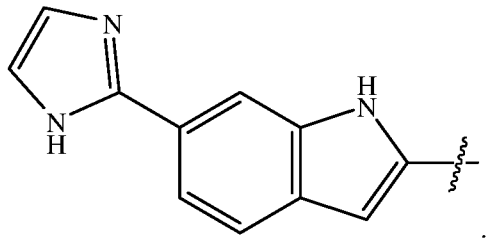
wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$.

In some specific embodiments at least one of the R is an imidazole derivative and a triazine derivative.

In some embodiments at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



.

In some specific embodiments the at least one of the R is an imidazole derivative.

In some specific embodiments the at least one of the R is a dihydroimidazole derivative.

In some specific embodiments at least one of the R is a dihydroimidazole derivative.

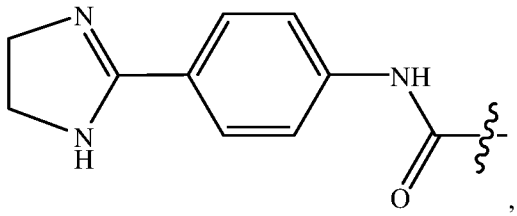
In some specific embodiments R is one or more dihydroimidazole derivative which may be the same or different.

In some further specific embodiments, the R of the compound of the present disclosure may be repeated n times. In some embodiments, n may be 2, 3, or 4.

In some specific embodiments n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

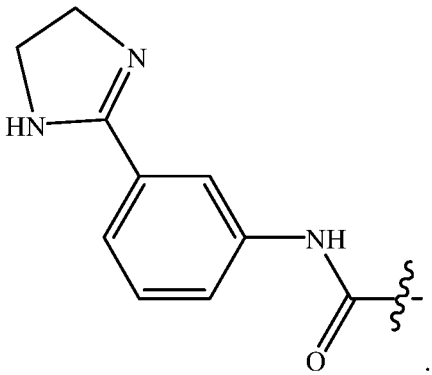
In some specific embodiments R is one or more dihydroimidazole derivative selected from

a)



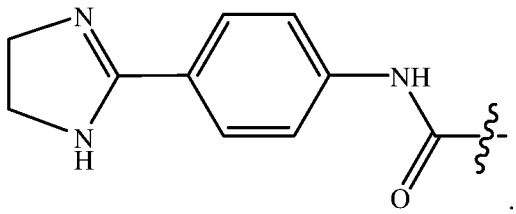
, or

b)



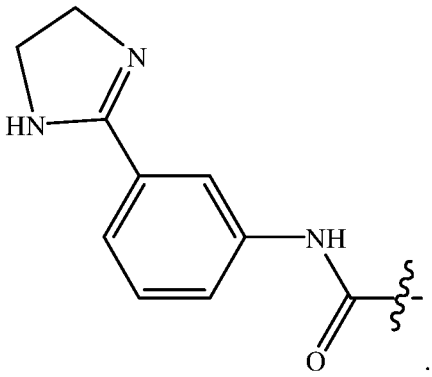
.

In some specific embodiments n may be 2 and each of R is the dihydroimidazole derivative



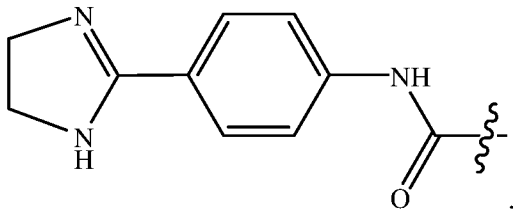
.

In some specific embodiments n may be 2 and each of R is the dihydroimidazole derivative



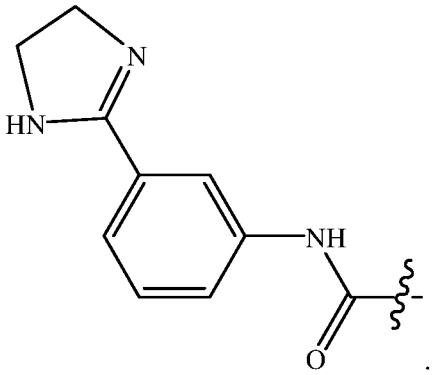
.

In some specific embodiments n may be 3 and each of R is the dihydroimidazole derivative



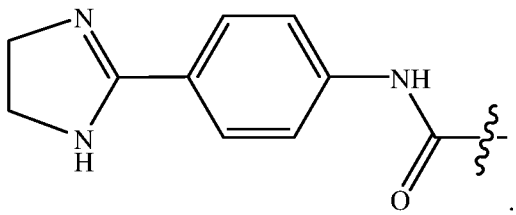
.

In some specific embodiments n may be 3 and each of R is the dihydroimidazole derivative



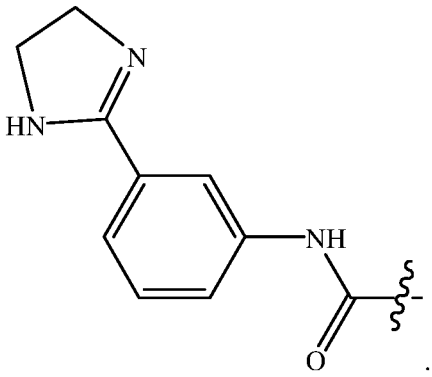
.

In some specific embodiments n may be 4 and each of R is the dihydroimidazole derivative



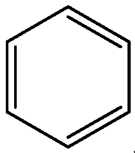
.

In some specific embodiments n may be 4 and each of R is the dihydroimidazole derivative



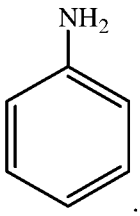
.

According to some embodiments, the compound of **Formula I** may comprise Ar that is:



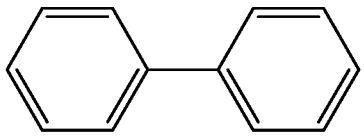
.

According to some further embodiments, the compounds of **Formula I** may comprise Ar that is:



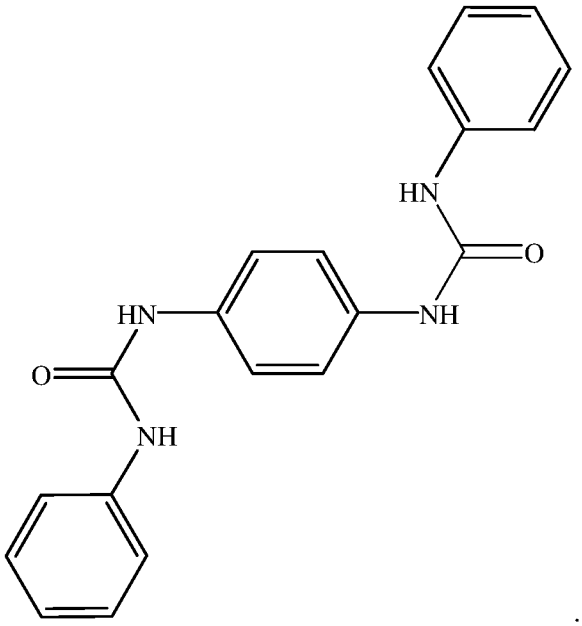
.

According to some embodiments, the compound of **Formula I** may comprise Ar that is:

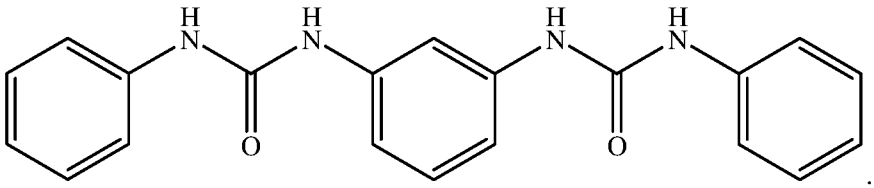


.

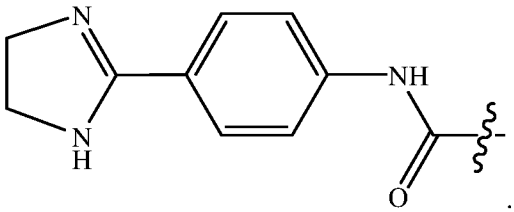
Still further, according to some embodiments, the compound of **Formula I** may comprise Ar that is:



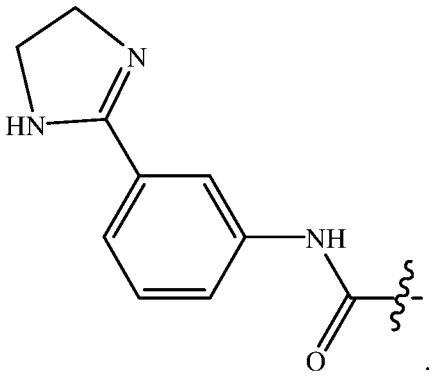
Still further, according to some embodiments, the compound of **Formula I** may comprise Ar that is:



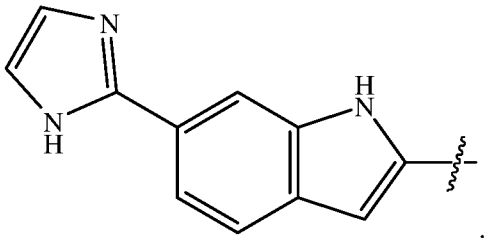
Still further, according to some embodiments, the compound of **Formula I** may comprise R that is:



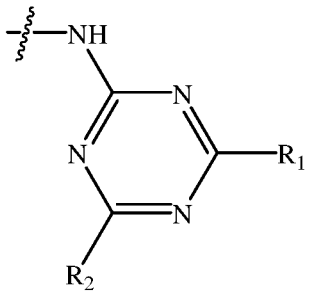
According to some further embodiments, the compound of **Formula I** may comprise R that is:



According to some embodiments, the compound of **Formula I** may comprise R that is:

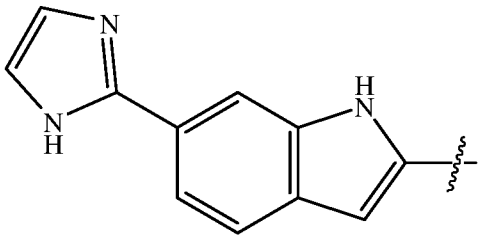


According to some embodiments, the compound of **Formula I** may comprise R that is:

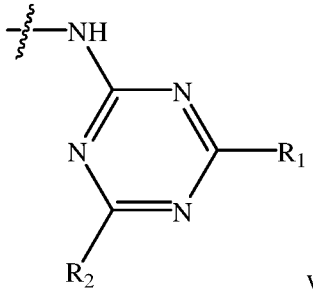


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine.

According to some embodiments, the compounds of **Formula I** may comprise R that is:

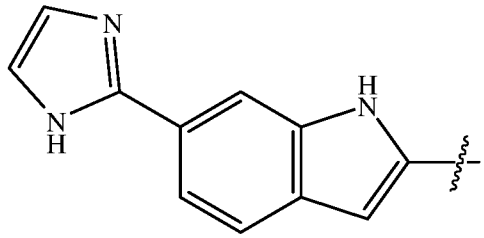


and R that is:

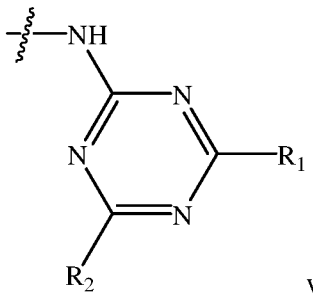


wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine.

According to some embodiments, the compounds of **Formula I** may comprise R that is:

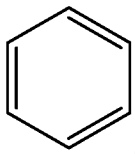


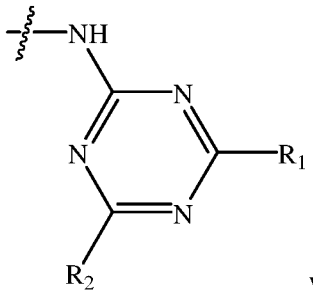
and R that is:



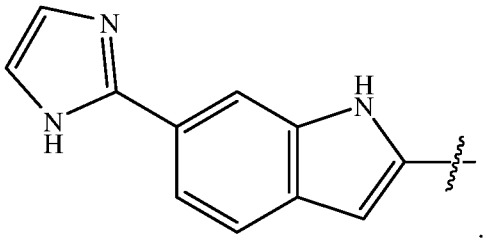
wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$.

Any combination of the above depicted one or more of said Ar and one or more of said R is within the scope of the presented disclosure.

For example, in some embodiments Ar is , at least one of R is



wherein R_1 is a halogen (e.g., Cl) and R_2 is $-NH_2$, and at least one of a further R is



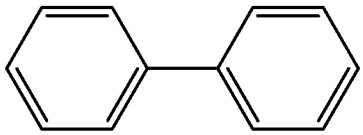
.

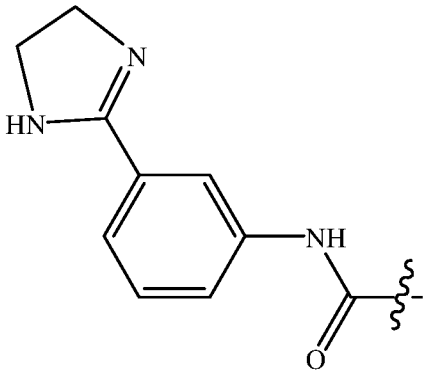
Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 2 and the two R groups may be oriented in para-position on the Ar group, relative to each other.

In some embodiments n is 2 and the two R groups may be oriented in meta-position on the Ar group, relative to each other.

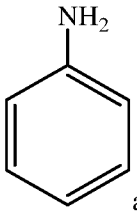
In some embodiments n is 2 and the two R groups may be oriented in ortho-position on the Ar group, relative to each other.

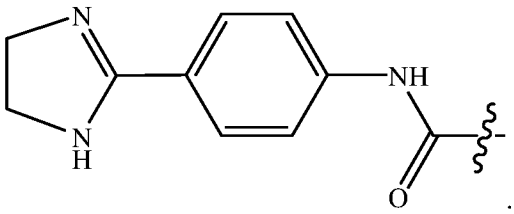
In some embodiments Ar is  and at least one of R is



Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 2 and the two R groups may be symmetrically oriented relative to each other on the Ar group.

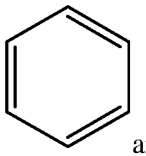
In some embodiments Ar is  and at least one of R is

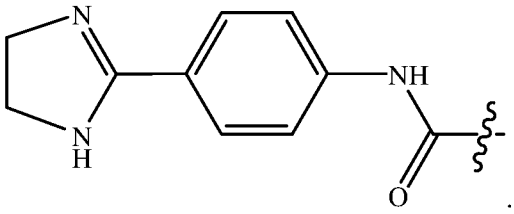


.

Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 2 and the two R groups may be para-oriented relative to each other on the Ar group.

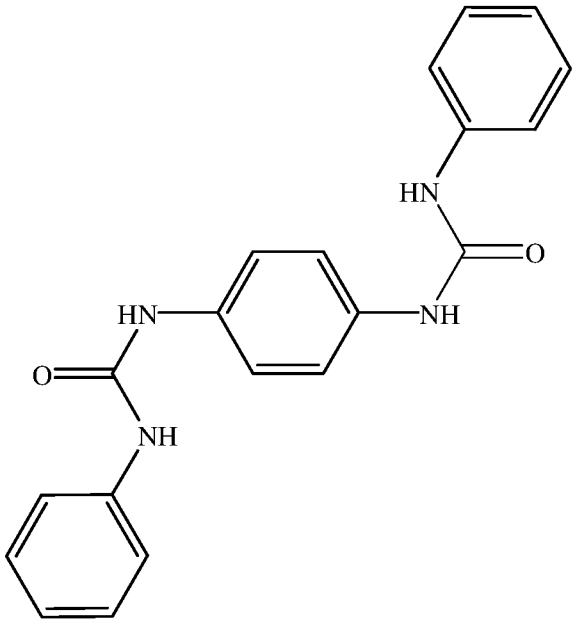
In some embodiments Ar is  and at least one of R is

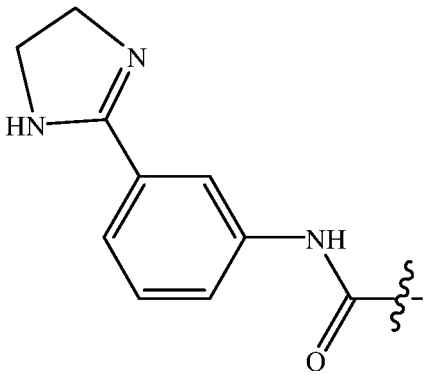


.

Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 3 and the three R groups may be meta-oriented relative to each other on the Ar group.

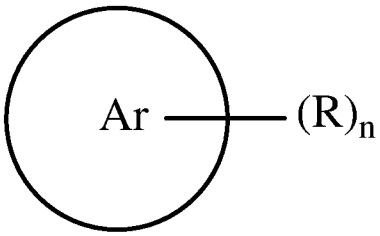
In some embodiments Ar is  and at least one of R is



Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 4 and the four R groups may be symmetrically oriented relative to each other on the Ar group.

Another aspect of the present invention relates to at least one small molecule compound of **Formula II**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or with any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any composition thereof, wherein said **Formula II** is:

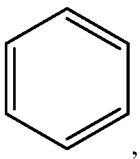


Formula II

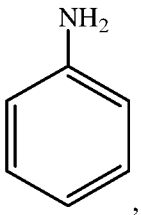
wherein Ar is an aromatic or heteroaromatic moiety; wherein R is a dihydroimidazole derivative; wherein each of said Ar and R may optionally be further substituted; wherein n is an integer from 1 to 10; and wherein when n>1, any one of the R may be the same or different, provided that said at least one small molecule compound of **Formula II** is not any one of compounds #1, #2, #3, #4 and #5, also disclosed herein as compounds of **Formulas IV**, **III**, **V**, **VI** and **VIII**, respectively.

In some embodiments the Ar of the compound of **Formula II**, may be selected from the group consisting of:

a)

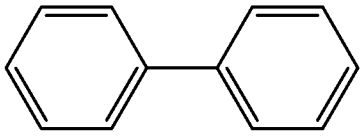

,

b)



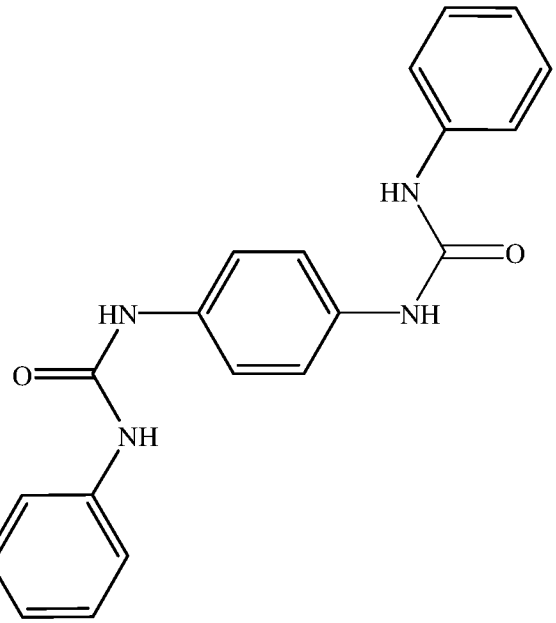
,

c)



, and

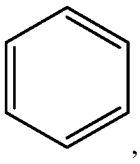
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

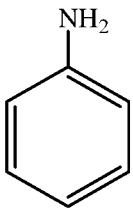
In some embodiments the Ar of the compound of **Formula II** is selected from the group consisting of:

a)



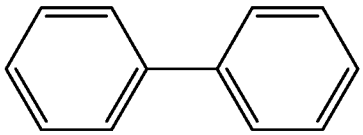
,

b)



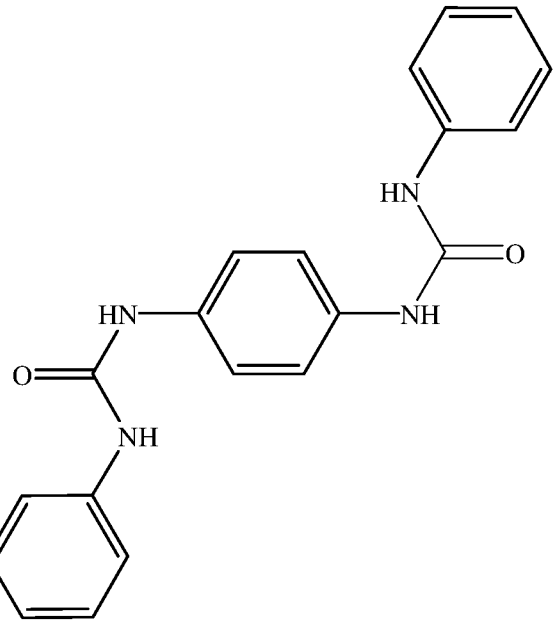
,

c)



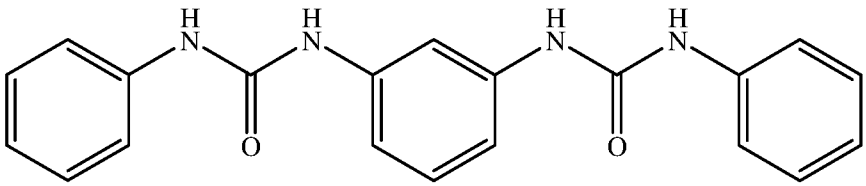
,

d)



, and

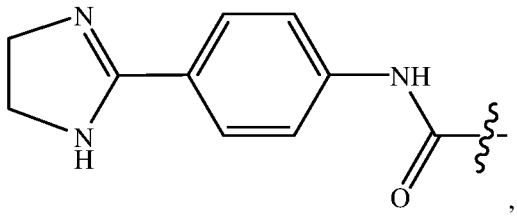
e)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

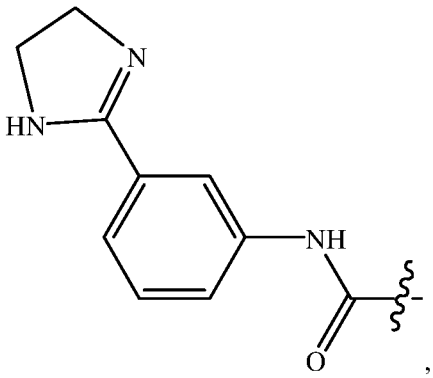
In yet some further embodiments the R of the compound of **Formula II**, may be selected from the group consisting of:

a)



, and

b)



, wherein each of said R may optionally be further substituted.

In some embodiments each of said R is not further substituted.

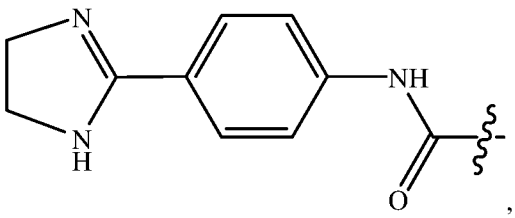
In some specific embodiments R is one or more dihydroimidazole derivative which may be the same or different.

In some further specific embodiments, the R of the compound of the present disclosure may be repeated n times. In some embodiments, n may be 2, 3, or 4.

In some specific embodiments n may be 2, 3, or 4, wherein R is one or more dihydroimidazole derivative, which may be the same or different.

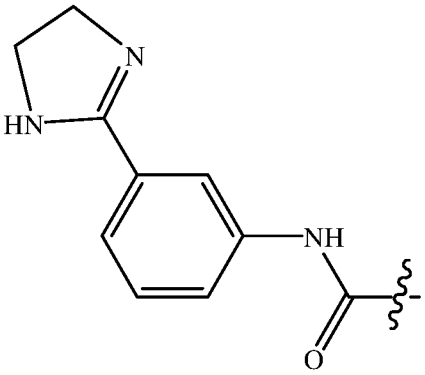
In some specific embodiments R is one or more dihydroimidazole derivative selected from

a)



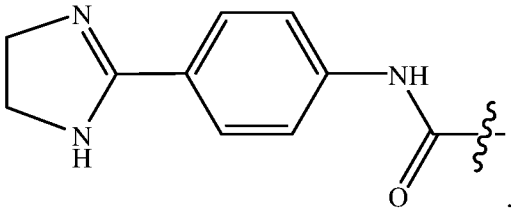
, or

b)



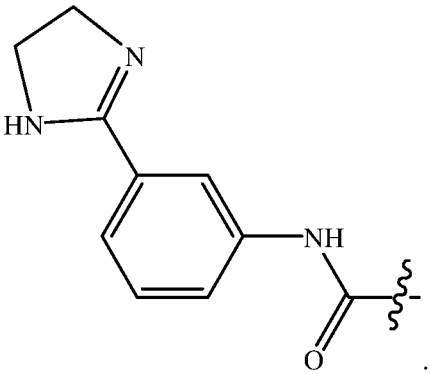
wherein each of said R may optionally be further substituted.

In some specific embodiments n may be 2 and each of R is the dihydroimidazole derivative



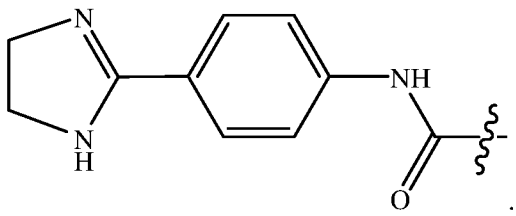
.

In some specific embodiments n may be 2 and each of R is the dihydroimidazole derivative



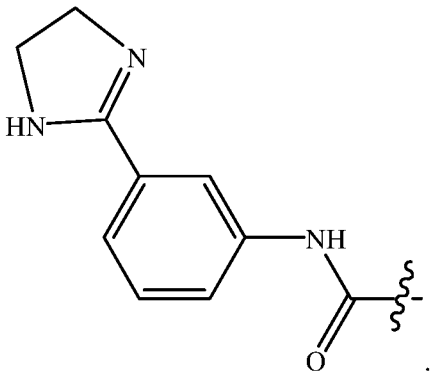
.

In some specific embodiments n may be 3 and each of R is the dihydroimidazole derivative



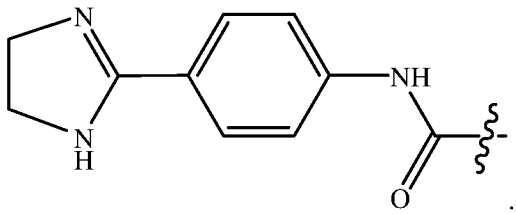
.

In some specific embodiments n may be 3 and each of R is the dihydroimidazole derivative



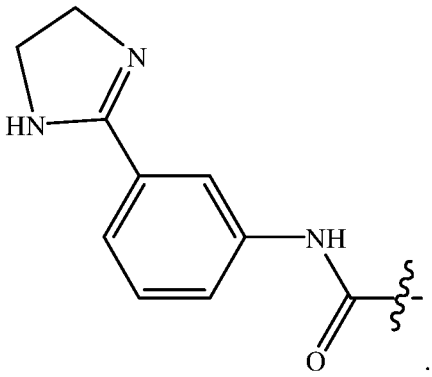
.

In some specific embodiments n may be 4 and each of R is the dihydroimidazole derivative

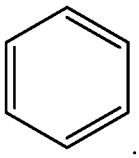


.

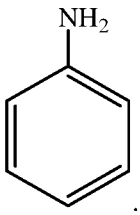
In some specific embodiments n may be 4 and each of R is the dihydroimidazole derivative



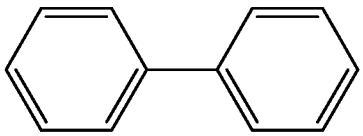
According to some embodiments, the compound of **Formula II** may comprise Ar that is:



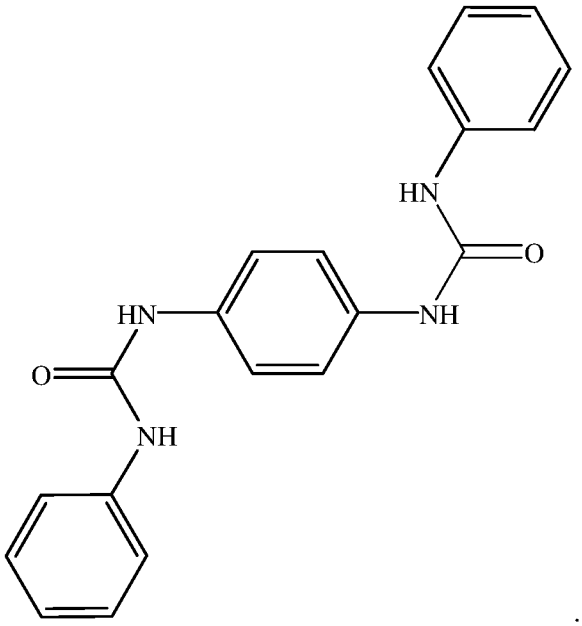
According to some further embodiments, the compounds of **Formula II** may comprise Ar that is:



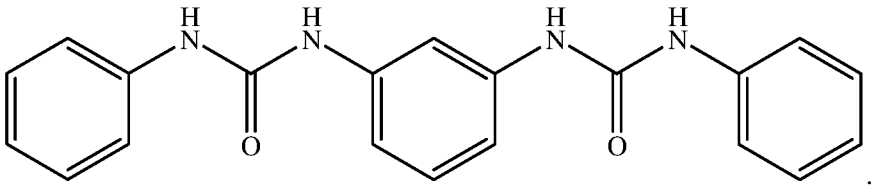
According to some embodiments, the compound of **Formula II** may comprise Ar that is:



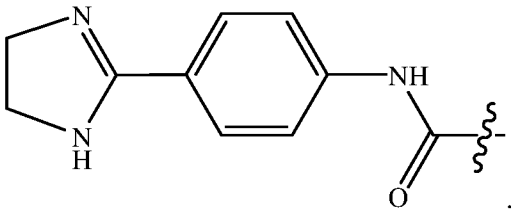
Still further, according to some embodiments, the compound of **Formula II** may comprise Ar that is:



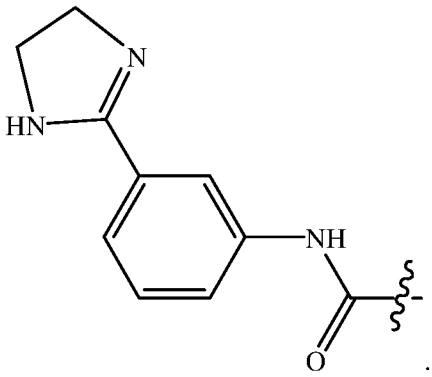
Still further, according to some embodiments, the compound of **Formula II** may comprise Ar that is:



Still further, according to some embodiments, the compound of **Formula II** may comprise R that is:



According to some further embodiments, the compound of **Formula II** may comprise R that is:



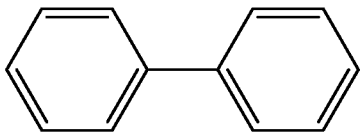
.

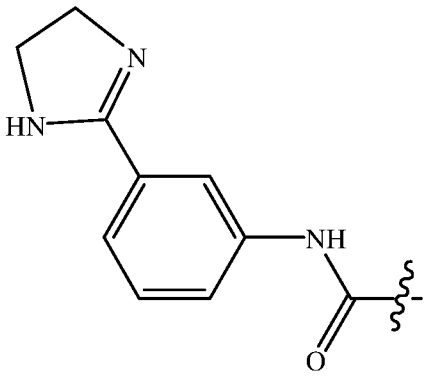
Any combination of the above depicted one or more of said Ar and one or more of said R is within the scope of the presented disclosure.

In some embodiments n is 2 and the two R groups may be oriented in para-position on the Ar group, relative to each other.

In some embodiments n is 2 and the two R groups may be oriented in meta-position on the Ar group, relative to each other.

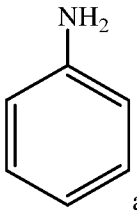
In some embodiments n is 2 and the two R groups may be oriented in ortho-position on the Ar group, relative to each other.

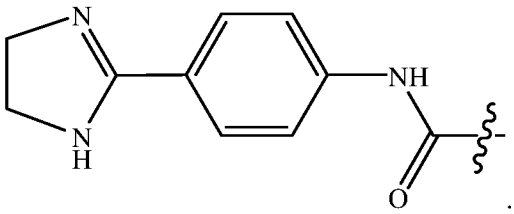
In some embodiments Ar is  and at least one of R is



Any one of said Ar and R may optionally be further substituted.

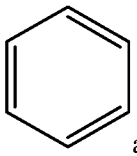
In some embodiments n is 2 and the two R groups may be symmetrically oriented relative to each other on the Ar group.

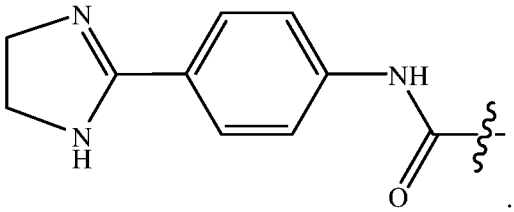
In some embodiments Ar is  and at least one of R is



Any one of said Ar and R may optionally be further substituted.

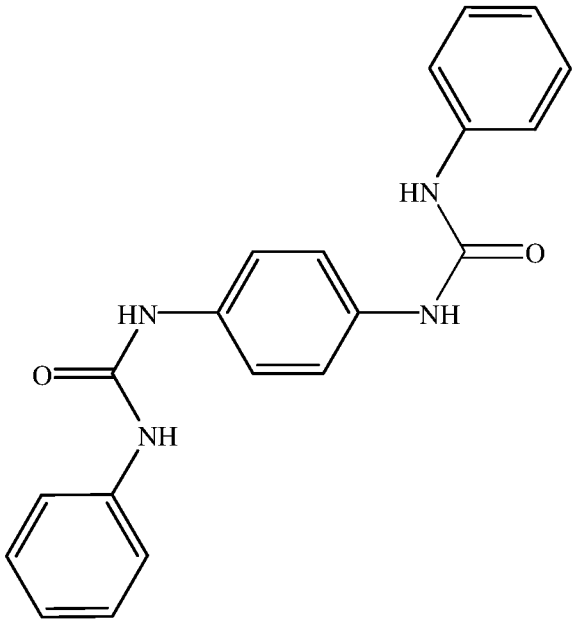
In some embodiments n is 2 and the two R groups may be para-oriented relative to each other on the Ar group.

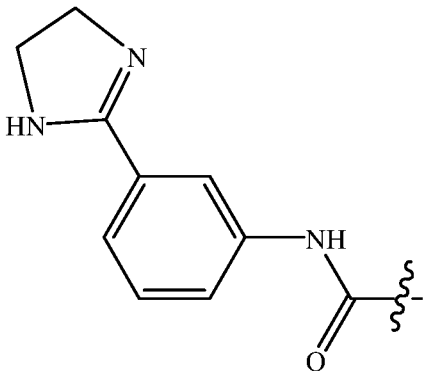
In some embodiments Ar is  and at least one of R is



Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 3 and the three R groups may be meta-oriented relative to each other on the Ar group.

In some embodiments Ar is  and at least one of R is



Any one of said Ar and R may optionally be further substituted.

In some embodiments n is 4 and the four R groups may be symmetrically oriented relative to each other on the Ar group.

All scientific and technical terms used herein have meanings commonly used in the art unless otherwise specified. The definitions provided herein are to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

As used herein the term "about" refers to ± 10 %. The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to". The term "consisting essentially of" means that the composition, method or

structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

The term "about" as used herein indicates values that may deviate up to 1%, more specifically 5%, more specifically 10%, more specifically 15%, and in some cases up to 20% higher or lower than the value referred to, the deviation range including integer values, and, if applicable, non-integer values as well, constituting a continuous range. As used herein the term "about" refers to ± 10 %.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to". This term encompasses the terms "consisting of" and "consisting essentially of". The phrase "consisting essentially of" means that the composition or method may include additional ingredients and/or steps, but only if the additional ingredients and/or steps do not materially alter the basic and novel characteristics of the claimed composition or method. Throughout this specification and the Examples and claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It should be noted that various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub ranges as well as individual numerical values within that range.

For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range. Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein

interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals there between.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub combination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated herein above and as claimed in the claims section below find experimental support in the following examples.

Disclosed and described, it is to be understood that this invention is not limited to the particular examples, methods steps, and compositions disclosed herein as such methods steps and compositions may vary somewhat. It is also to be understood that the terminology used herein is used for the purpose of describing particular embodiments only and not intended to be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

It must be noted that, as used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the content clearly dictates otherwise.

EXAMPLES

Experimental procedures

Cell culture

The following cell lines were obtained from ATCC: TNBC MDA-MB-231, BT-549, HCC70 and Hs578T; Melanoma SK-MEL-24, RPMI-7951 and MDA-MB-435; Pancreatic cancer AsPC-1, BxPC-3 and CFPAC-1; NSCLC A-549, NCI-H1299, NCI-H1975 and NCI-H2030; Liver hepatocarcinoma SK-HEP1. They were routinely cultured according to ATCC "culture method" at 37°C in 5% CO_2 each in its recommended medium supplemented with 5%-10% fetal bovine serum (FBS) (Biological Industries), 10 units/ml of penicillin and 50 µg/ml streptomycin.

RNA Extraction from cell culture

Total RNA of the different cultures was extracted using Quick-RNA™ MiniPrep Kit (Zymo, ZR-R1055) according to the manufacturer instructions. RNA concentration and RNA quality were determined by SpectraMax quick drop micro-volume spectrophotometer (Molecular Devices).

Reverse Transcription (RT)

Reverse transcription was carried out using RevertAid™ Premium kit (Thermo Fisher), using hexamer primers and according to the manufacturer instructions. Usually, 1 µg of RNA was subjected to reverse transcription reaction in 20 µl. In order to identify promoter-spanning lncRNAs of antisense orientation (so it is not mixed with plausible upstream-initiating protein coding transcripts) total cellular RNA/nuclear RNA from the human tumor cell lines, were subject to primer-specific RT-PCR.

Quantitative Real-Time PCR

RNA level was assessed using the TaqMan Gene Expression Assay (Applied Biosystems) and a QuantStudio 1 RT-qPCR System (Thermo Fisher) following the manufacturer-recommended procedures. TaqMan® PCR took place in 96-well reaction plates holding a volume of 10 µL in each well. The mixture consisted of TaqMan® Gene Expression Assay 20× (Thermo Fisher Scientific), TaqMan® Universal PCR Master Mix 2× (Thermo Fisher Scientific), and 30ng of desired cDNA. The $2^{-\Delta\Delta^{CT}}$ method was used for quantification of the relative RNA expression applying HMBS as the normalizing housekeeping gene. Each sample was validated three times (n=3).

Compounds effect on KAI1 mRNA and SKAI1BC lncRNA level

Cells were treated with 5µM of each of the compounds (#1, #2, #3, #4, and #6, also disclosed herein as Formulas IV, III, V, VI and VII, respectively) for 48h, their total RNA was extracted and reverse-transcribed to cDNA. Relative KAI1 mRNA expression, as well as SKAI1BC lncRNA were quantified by Real-Time PCR with HMBS RNA as endogenous normalizing control.

Cell Counting

Cells were detached from culture dish in Trypsin–EDTA. Cells were counted automatically using EVE cell counter (NanoEnTek) after the addition of trypan blue.

Cell proliferation assay

Cells were seeded evenly at the magnitude of about 10^5 cells/ml into a 6-well plate. The cells were incubated with the medium alone or with the addition of 5uM of the different compounds. After 48 h of incubation the cells were harvested, trypan blue was added and the cells counted. Each experiment was performed three times, and the average values calculated and used for the appropriate figures.

Cell Migration Assay

To study cell migration, cells were treated with 5µM of each of the compounds (#1, #2, #3, #4 and #6) for 24h. Then, ThinCert™ (Greiner Bio-One) cell culture inserts were placed in a multi well cell culture plate. The insert contains a polyethylene terephthalate (PET) membrane at the bottom with a pore size of 8 µm that separates the upper from the lower compartment. Of the pre-treated cells, 100,000 serum-starved cells were seeded at the top of the insert in 200 µl serum free media, with or without 5uM of the different particular compound. The lower compartment contains 10% FBS media as a chemo-attractant that may induce active migration of the seeded cells through the PET membrane. Adherent cells that migrate through the pores remain attached to the under-side of the PET-membrane. After 24 hours, the medium in the inserts and lower compartment was removed. To estimate the percentage of migrated cells, a Resazurin Cell Viability Assay is performed and compared to the mock control cells.

Cell Invasion assay

Cells were treated with 5µM of each of the compounds (#1, #2, #3, #4 and #6) for 24h. Cells were then seeded in CytoSelect (CBA-110, Cell Biolabs) transwell chambers for additional 24h, while under starvation conditions, and in the presence of the compounds. Cells invasion from the upper chamber to the chemoattractant (10% serum)

in the lower chamber were quantified using colorimetric assay and according to the manufacturer instructions.

Comparison of gene expression pathways affected in TNBC cells by Compound #3 (Formula V) vs. by Compound #6 (Formula VII)

TNBC MDA-MB-231 cells were grown in six well plates and treated with either 0.05% DMSO as a mock, or 5uM of either Compound #3 or Compound #6. Forty-eight hours later, RNA was extracted from a six well plate using 1 ml of Trireagant (T9424) according to manufacturer's instructions. RNA concentration and purity was measured with Nano drop to verify QC 1.8-2.2 for 260/230 and 260/280. RNA integrity was examined on Tapestation 2200 (Agilent) using RNA Tape and Buffer (Agilent RNA SCREEN TAPE 5067-5576, RNA SCREEN TAPE SAMPLE BUFFER 5067-5577) and confirmed to be >9.5 for all samples.

Poly(A) selection was performed with kit NEX Poly(A) beads 2.0 (48 rxn)-NOVA-512992 (Perkin Elmer) using 1.2ug according to manufacturer's instructions and eluted in 14ul. Enriched RNA was used for RNA library preparation NEXTFLEX Rapid XP DNA-seq Kit (96rxn)-514903 (Perkin Elmer) according to manufacturer's instructions using 15 minutes fragmentation and 10 cycle amplification. cDNA was quantified using DSDNA HIGH SENSITIVITY 1000 RXN-DSDNA-H2 and quality was assessed with Tapestation (D1000 SCREEN TAPE 5067-5582 and D1000 REAGENTS 5067-5583) to determine band specificity and size.

Libraries were pooled and sequenced on a Hiseq (Illumina). Samples were demultiplexed using Bcl2FastQ and phred score quality was measured using fastqc and multiqc to be >30 for >87% of all samples.

Samples were aligned to Hg38 genome using STAR with default parameters. Mapping quality was examined using SeqMonk and >85% were found to map to exons, with no rRNA or mDNA contamination. Samples were quantified using htseqcount and compared using Deseq2 with default parameters. Pathways analysis was performed using ClusterProfiler tool, using genes with a >=1.5-fold change and significance of 0.1FDR to obtain enriched GO terms and KEGG pathways.

Generation of TNBC-derived spontaneous metastasis in mice in vivo and testing their response to the compounds

Initially, female BALB/cOlaHsd-Foxn1nude immune-deficient mice (7-8 weeks old) were injected subcutaneously with 2x10^5 TNBC MDA-MB-231-luciferase2 cells (in a

volume of 50 ul while being in PBS) into the fourth mammary fat pad (MPF), close to the base of the nipple. Then every other day on Sunday, Tuesday and Thursday every week the mice are injected i.p. with either 0.2 ml of PBS, 50 mg/kg mice of PBS-soluble compound #2 (**Formula III**), or 37.5 mg/kg mice of compound #2 while comparing via the bioluminescence monitoring the drug effect on metastasis formation. Metastasis is monitored twice a week by bioluminescence, while comparing the luminescence of the formed metastases. For this purpose, an IVIS 200 Xenogen, is being used a few minutes after the mice were anaesthetized and injected 3 mg of D-luciferin in PBS.

By shielding the metastatic sites from the primary breast tumor in the fourth MPF (located in the lower half of the animal), the extent of tumor spread to the lymph nodes lung and brain can be quantified by bioluminescence in real time, in vivo. Also CT scanning to identify metastases is being used.

EXAMPLE 1

Predicting the structure of the SKAI1BC lncRNA and computational screening for potential KAI1 as-lncRNA binding molecules

To assess the draggability of the 792 bp long KAI1 as-lncRNA, the inventor used the RNAfold of ViennaRNA package program to predict, via free energy minimization, the secondary structure of the lncRNA. Sliding windows of 150 nt sequences were folded every 10 nt from the 5′ end. The free energy of each sequence was calculated, followed by a z-score for its difference compared to the average free energy of 50 randomized sequences for each window. Folded sequences whose z-scores were more than one standard deviation below the average z-score for all folded sequences were defined as "strict" regions that were more likely to form stable or conserved structures more stable than those formed from randomized sequences. The ensemble diversity was calculated to determine the diversity of alternative folds, while lower numbers suggest that the sequences will more likely form into single structures. Sequences from these regions were compiled and folded to generate a new set of structures. These regions likely form well-defined structures that inform on possible protein-binding sites and therapeutic targets. The 792 nt SKAI1BC lncRNA construct yielded four structured regions ranging from 160 nts to 200 nts in length (**Figure 1**). Specifically, the nts 381-640 (**Fig. 1C**) region is the most stable ($\Delta G^\circ = -112.9$ kcal).

These presumably targetable small structures were compared to the RNA motifs-small molecule interactions InfoRNA 2.0 database, which was generated experimentally primarily by the inventor's group (Disney et al., 2016). The Inforna search yielded five compounds (#1-#5, also denoted by **Formulas IV, III, V, VI,** and **VIII**) with fitness scores of at least 70% for each region, the top hits among which are shown in **Figure 2A-2D**. For example, the 5'CAU/3'G_A, 5'GCG/3'C_C, 5'GUC/3'C_G, 5'CCU/3'G_A bulge loops in these regions were predicted to bind to a similar set of compounds with fitness scores up to 100%, indicating that a particular compound may be able to inhibit multiple sites on the human SKAI1BC lncRNA. The compounds were tested together with another compound #6 that was not predicted to bind KAI1 as-lncRNA.

EXAMPLE 2

Testing the compounds on TNBC cell lines

Compounds #1, #2, #3, #4 and #6 (also disclosed herein as **Formulas IV, III, V, VI** and **VII**, respectively) were assayed at 5uM concentration for stimulating the RNA level of the KAI1 metastasis suppressor in TNBC cell lines (**Figure 3**). The results show that 4 out of the 5 compounds (compounds #1-#4 at 5uM) stimulated KAI1 RNA expression by up to 2.0-2.2- fold in the TNBC MDA-MB-231 and BT-549 **(Figure 3A(i)** upper row), HCC70 and Hs578T cell lines (**Figure 3B(i)** upper row). The extent of KAI1 RNA stimulation was both compound- and cell line-dependent. For example, the non-metastatic MCF10A cell line served as the negative control to these experiments and did not respond at all (Data not shown). According to the computational screening disclosed in Example 1, Compound #6 that was predicted not to bind KAI1 as-lncRNA, did not stimulate KAI1 RNA level in the four TNBC cell lines (**Figures 3A(i), 3B(i)**). Moreover, incubation of these four compounds at 5uM for 48 hours with each of these TNBC cell lines resulted in severe inhibition of metastasis cell invasion, typically from 54%-94% (**Figure 3A(ii)-3B(ii),** middle row). Interestingly, compound #6 inhibited cell invasion of all four TNBC cell lines, even though it did not boost KAI1 RNA level in MDA-MB-231, BT-549, HCC70 and Hs578T (**Figure 3A(ii)-3B(ii),** middle row). In contrast, none of the five compounds inhibited the very modest invasion of the MCF10A derived cells (data not shown). These experiments where followed by inquiry of the compounds effect on cell migration, the second step of metastasis following cell invasion. As shown (**Figure 3A(iii)-3B(iii),** bottom row), all four tested TNBC cell

lines (MDA-MB-231, BT-549, HCC70 and Hs578T) had their cell migration inhibited (from 30%-89%) by each of the five compounds, including compound #6. So, based on compound #6 reactions, inhibition of cell invasion and migration can be triggered not only by elevation of the KAI1 metastasis suppressor RNA, but also by other mechanism/s.

EXAMPLE 3

Testing the compounds on Breast Cancer cell-lines

In MCF-7 (Luminal A), ZR-75-30 (Luminal B) and SkBr3 (HER2+) cell lines (**Figure 4(i),** upper row), there is no significant stimulation of KAI1 RNA level by each of the five compounds (#1-#4 and #6). Testing invasion, the five compounds managed to inhibit cell invasion in all three Breast cancer cell lines (**Figure 4(ii),** middle row). Moreover, in these cell lines there was also cell migration inhibition triggered by all five compounds except from #4 and #6 in ZR-75-30 (Luminal B) **Figure 4(iii),** bottom row). The lack of stimulation in KAI1 RNA level in compounds treated cells, clearly demonstrates that depending on the cell line, inhibition of metastasis cell invasion and migration can occur even in the absence of the metastasis suppressor KAI1 RNA enhancement; apparently via a different mechanism.

EXAMPLE 4

Testing the compounds on Melanoma cell lines

In SK-MEL-24 and MDA-MB-435 cell lines (**Figure 5(i),** upper row), there is significant stimulation of KAI1 RNA level by each of the four compounds (#1-#4). With compound #6 there is a minor elevation in KAI1 RNA level. In the RPMI-7951 cell line, on the other hand, there is no KAI1 RNA stimulation (**Figure 5(i),** upper row). Testing invasion, the five compounds managed to inhibit cell invasion in all three Melanoma cell lines including in RPMI-7951 (**Figure 5(ii),** middle row). Moreover, in these Melanoma cell lines there was also cell migration inhibition triggered by all five compounds (**Figure 5(iii),** bottom row).

The different pattern of KAI1 RNA level in compounds treated RPMI-7951 cells, clearly demonstrates again that depending on the cell line, inhibition of metastasis cell invasion and migration can occur even in the absence of the metastasis suppressor RNA enhancement, apparently via a different mechanism.

Interestingly, concentration curve of molecule #2 (Formula III) for example, in the melanoma MDA-MB-435 cells inhibited invasiveness by 81% at 5uM, and still by 23% at 50 nM; implying a very potent cell invasion inhibition by this compound.

EXAMPLE 5

Testing the compounds on pancreatic cancer cell lines

AsPC-1, BxPC-3 and CFPAC-1 are the three pancreatic carcinoma cell lines tested with the five compounds at 5uM in this work (**Figure 6(i)-(iii)**). KAI1 RNA level in AsPC-1 and BxPC-3 was elevated by all compounds, while in CFPAC-1 only compounds #3, #4 and #6 stimulated the KAI1 RNA level (**Figure 6 (i)**). Yet, all compounds triggered significant metastasis cell invasion inhibition, as well as inhibiting cell migration in all three cell lines (AsPC-1, BxPC-3, CFPAC-1, see **Figure 6 (ii), (iii),** middle and bottom rows).

EXAMPLE 6

Testing the compounds on NSCLC cell lines

A-549, NCI-H1975, NCI-H1299 and NCI-H2030 are the Non-Small Cell Lung Carcinoma (NSCLC) derived cell lines tested in this work. The NCI-H1975 and NCI-H2030 cell lines responded, generally speaking, better to the compounds than the other two cell lines, in terms of KAI1 RNA stimulation (**Figure 7A(i)-7B(i),** upper row). Yet, all five compounds inhibited invasion and migration in all four cell lines irrespective whether they induced KAI1 RNA production or not (**Figure 7(ii), (iii),** middle and bottom row). This observation again demonstrates that there are at least two anti-metastatic mechanisms shared by the five compounds: one, which acts via KAI1 RNA elevation, the other independent of KAI1 gene expression enhancement.

EXAMPLE 7

Testing the compounds on Liver Carcinoma derived cell lines

SK-HEP1 and C3A are the Liver Cell Carcinoma tested in this work. In SK-HEP1 cell line only compound #4 induced KAI1 RNA stimulation (by x1.7), whereas in C3A compounds #1 and #3 stimulated KAI1 RNA by x3.5 and x2.7, respectively (**Fig. 8(i),** upper row). Yet, all five compounds inhibited invasion and migration in both cell lines irrespective whether they induced KAI1 RNA production or not (**Figure 8(ii), (iii).**

middle and bottom row). This observation again demonstrates that there are at least two mechanisms shared by the five compounds: one, which acts via KAI1 RNA elevation, the other independent of KAI1 gene expression enhancement.

EXAMPLE 8

Testing the compounds effect on proliferation of various cells lines

The effect of the disclosed compounds on proliferation of the TNBC, Breast Luminal A, Breast Luminal B & $HER2^+$ Breast cancers, Melanoma, Pancreatic Cancer, NSCLC and Liver cancer cell lines was next tested.

The TNBC cell lines MDA-MB-231, HCC70, the Breast cancer: MCF-7 (Luminal A), ZR-75-30 (Luminal B) and SkBr3 (HER2+), the melanoma cell lines SK-MEL-24 and RPMI-7951, the pancreatic cancer cell lines AsPC-1 and CFPAC-1, and the NSCLC cell lines NCI-H1299 and NCI-H2030, the liver cancer cell lines SK-HEP1 and C3A are of metastatic origin. The cell lines were tested for compounds mediated cell amplification sensitivity. For this purpose, cells were incubated for 48 hours with each of compounds #1-#4 and #6 at 5uM, as well as with DMSO mock as a control, and then viable cells were counted by a cell counter as outlined above. Overall, none of the nine cell lines were severely inhibited, or over-grown **(Figures 9-14)**. Results show that compound #3 inhibited TNBC cell line MDA-MB-231 by 3%. Compound #4 boosted the same cell line growth by 10% **(Figure 9)**. Compound #1 inhibited melanoma cell lines SK-MEL-24 and RPMI-7951 by 3% and 8%, respectively. While compound #4 increased both cell lines growth by 11% **(Figure 11)**. Compound #6 inhibited pancreatic carcinoma cell lines AsPC-1 and CFPAC-1 by 5% and 7%, respectively **(Figure 12)**. Compounds #1, #2, and #3 inhibited the NSCLC NCI-H1299 cell line by 9%, 8% and 7%, respectively **(Figure 13)**. Similar results were also demonstrated in liver cancer cell lines SK-HEP1 and C3A **(Figure 14)**.

EXAMPLE 9

Comparing the gene expression pathways affected in TNBC cells between compound #3 vs. compound #6

Comparison of the genes expression pathways in TNBC MDA-MB-231 cells treated by Mock vs by Compound #6 revealed 12 pathways which are inhibited significantly by Compound #6 with FC -1.5 till -2.14, while the pValues are less than 0.05. Among

these pathways are several known to participate in human metastasis, such as Cell Adhesion and TGF-beta.

The gene expression pathways were next compared between TNBC MDA-MB-231 cells treated by Compound #3 vs. Compound #6. When one considers only the pathways in which the pValue is less than 0.05, then there are 40 pathways which Compound #6 inhibits more than Compound #3, with FC ranging from -1.5 till -3.04. Among these pathways are several known to participate in human metastasis, such as Cell Adhesion, mTOR signaling, PI3K-Akt signaling, and WNT signaling.

These data indicate that while Compounds #1-#4 suppress metastasis of TNBC cell lines via enhancement of KAI1/CD82 RNA (Figs 3A and 3B), Compound #6 does it in TNBC through other pathway/s, as outlined above.

EXAMPLE 10

Testing compound #2 for inhibition of spontaneous metastasis in TNBC MDA-MB-231 mouse xenografts

In order to test the compounds effect *in vivo* on spontaneous metastasis in immune-deficient mice, the TNBC MDA-MB-231-Luc2 cell line is being used. Importantly, this cell line had been infected with the lentiviral vector TGL encoding for GFP, Firefly luciferase, and the human herpesvirus 1 TK. So, metastasis development can be monitored in the animals by either bioluminescence or fluorescence measurement. For metastasis generation in xenografted mice, female BALB/cOlaHsd-Foxn1nude mice (7-8 weeks old) were injected with 2x10^5 TNBC MDA-MB-231-Luc2 cells (in a volume of 50 ul while being in PBS) into the fourth mammary fat pad (MPF), close to the base of the nipple. Then every other day on Sunday, Tuesday and Thursday, every week, the mice are injected i.p. with either 0.2 ml of PBS, 50 mg/kg mice of PBS-soluble compound #2, or 37.5 mg/kg mice of compound #2. The drug effect is monitored via the bioluminescence effect on the primary tumors vs. on metastasis formation. Bioluminescence is monitored twice a week on Monday and Wed. using an IVIS 200 Xenogen; a few minutes after the mice were anaesthetized and injected 3 mg of D-luciferin in PBS. Spotting of the metastases is also monitored via CT scanning.

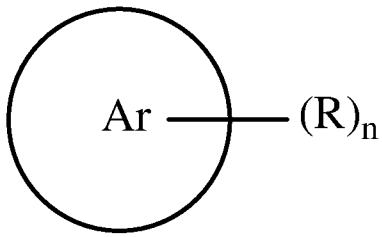
EXAMPLE 11

Generation and testing of TNBC Patients-Derived Xenografts (PDXs) to said compounds

As outlined above the five mentioned compounds were initially shown, to inhibit at low concentration, both TNBC and NSCLC metastasis cell invasion and cell migration, without affecting cell proliferation. Currently using the same tumours-derived cell lines, the inventors examine whether these compounds affect metastasis developed in Cell Derived mouse Xenografts (CDXs). Yet, in view of the known disadvantages of using human cell lines passaged for a long time, the infrastructure needed for PDX studies is in preparation (DeRose et al., 2011; Jung J et al., 2018). Initially, slices of TNBC primary tumours and/or metastases, 1-2 mm^3, are being received from the three Tel Aviv University affiliated hospitals. These are transplanted orthotopically to the fat pads of NOD/SCID female mice. Once these tumours reach enough size, they are dissected and re-implanted into another such mice. After 4-5 such serial transplantation of tumor grafts, PDX mice are ready for evaluating the response of their spontaneous metastasis to Compounds such as #1, #2, or #6. CT scanning coupled with surgical histology, is used to monitor spontaneous metastasis.

CLAIMS:

1. A method for the inhibition and/or reduction of at least one metastatic property of a cell, the method comprising the step of contacting said cell with an inhibitory effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or with any vehicle, matrix, nano-, micro-particles thereof, or any conjugates thereof, wherein said **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety;

wherein R is an imidazole derivative and/or triazine derivative;

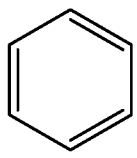
wherein each of said Ar and R may optionally be further substituted;

wherein n is an integer from 1 to 10; and

wherein when n>1, any one of said R may be the same or different.

2. The method according to claim 1, wherein Ar is selected from the group consisting of:

a)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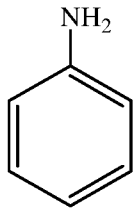
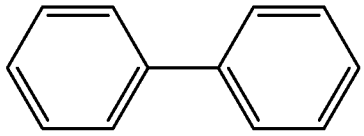
b)



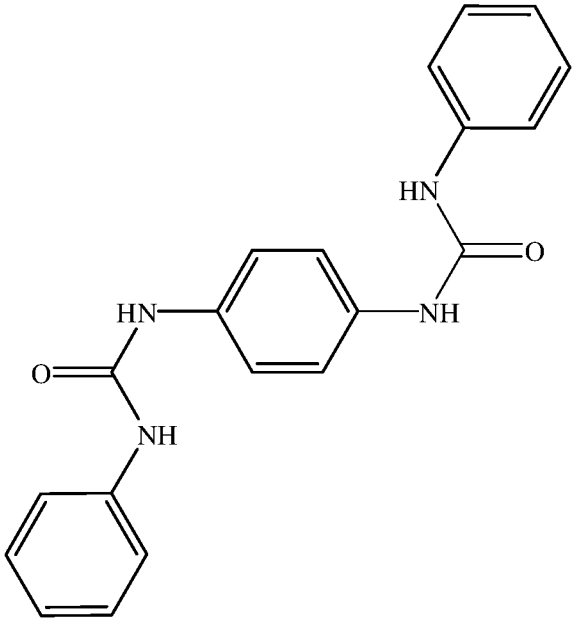
,

c)



, and

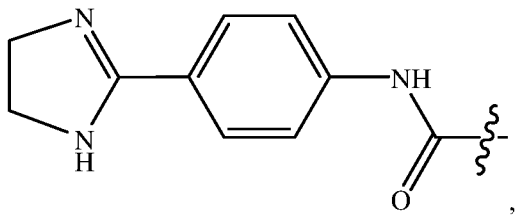
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

3. The method according to any one of claims 1 or 2, wherein R is selected from the group consisting of:

a)



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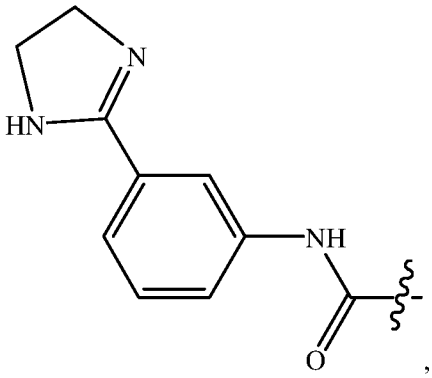
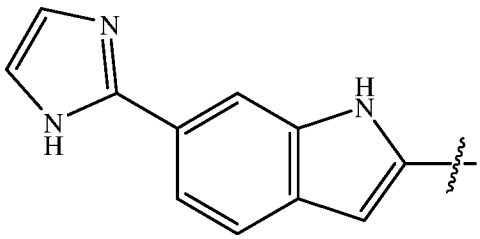
b)



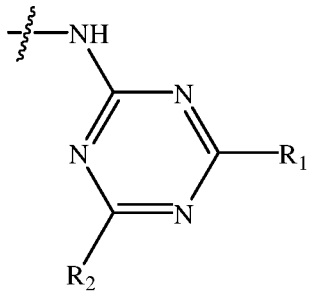
,

c)



, and

d)



wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine;

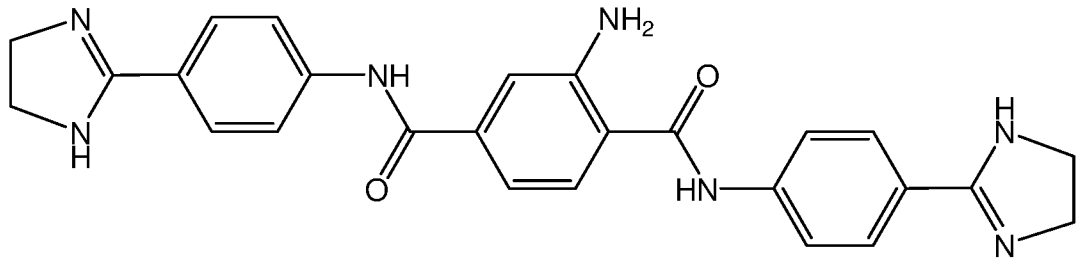
and wherein each of said R may optionally be further substituted.

4. The method according to any one of claims 1 to 3, wherein at least one of the said R is an imidazole derivative.

5. The method according to any one of claims 1 to 4, wherein n is 2, 3, or 4.

6. The method according to any one of claims 1 to 5, wherein said compound is at least one of:

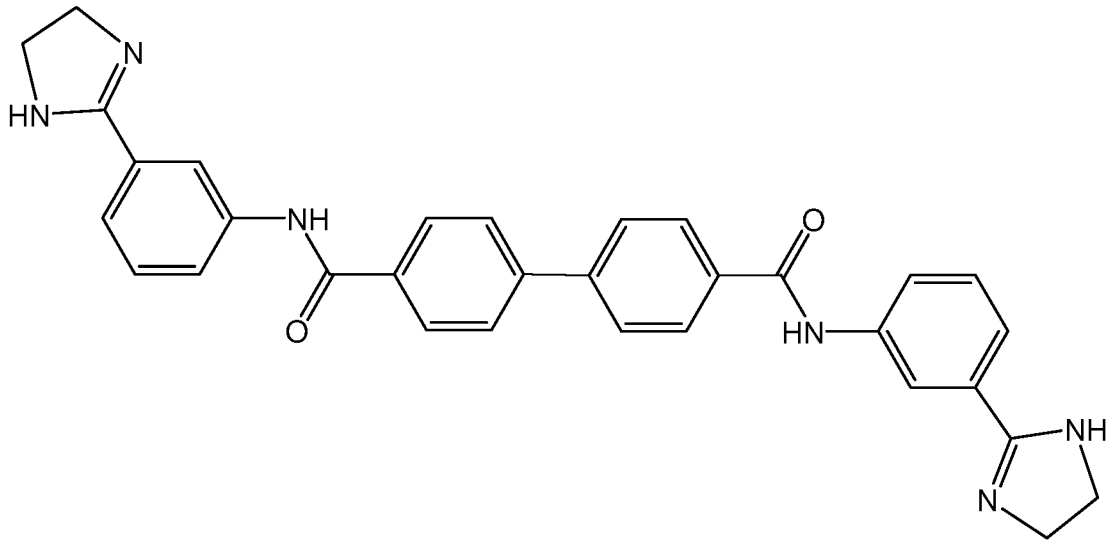
(a)



Formula III

a salt thereof, or any conjugates thereof;

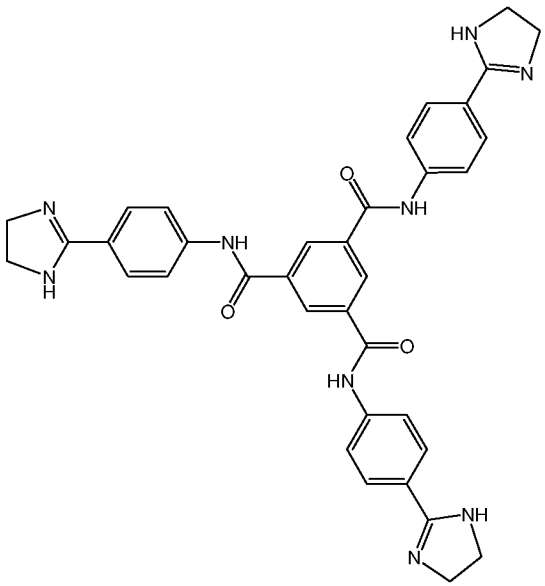
(b)



Formula IV

a salt thereof, or any conjugates thereof;

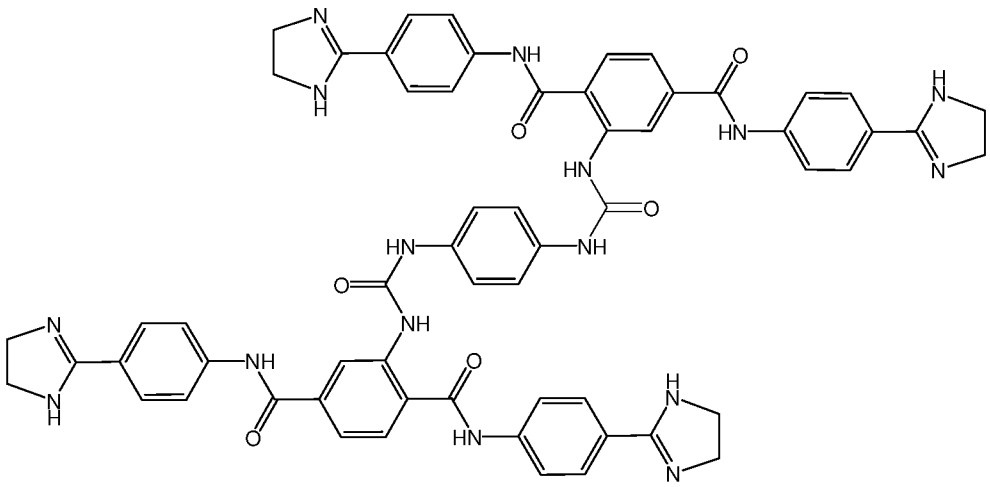
(c)



Formula V

a salt thereof, or any conjugates thereof;

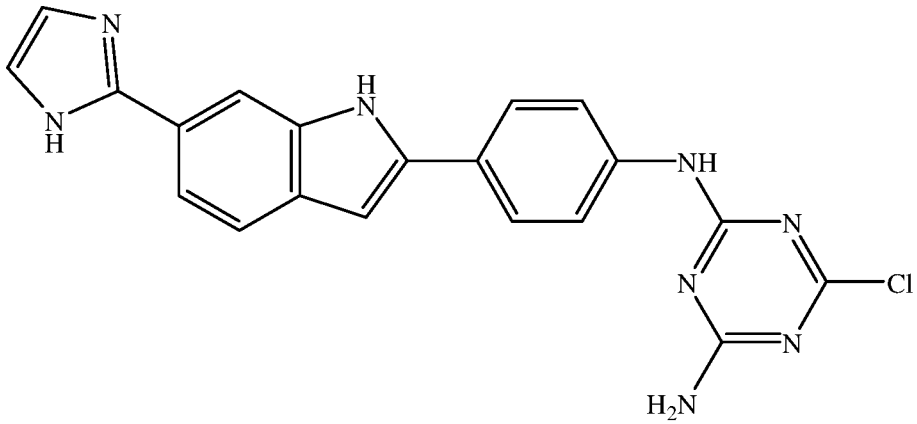
(d)



Formula VI

a salt thereof; and

(e)



Formula VII

a salt thereof, or any conjugates thereof.

7. The method according to any one of claims 1 to 6, wherein said metastatic property is at least one of cell invasiveness, cell motility, cell migration and cell adhesion.

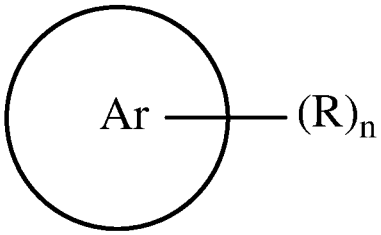
8. The method according to any of claims 1 to 7, wherein said cell is a mammalian malignant cancer cell.

9. The method according to any of claims 1 to 8, wherein said mammalian malignant cancer cell is originated from at least one of breast tissue, kidney tissue, hepatic tissue, pancreatic tissue, colorectal tissue, gastric tissue, lung tissue, skin tissue, ovarian tissue, prostate tissue, thyroid tissue, cervical tissue, endometrium tissue, laryngeal tissue, bone tissue and hematopoietic tissue.

10. The methods according to any of claims 1 to 9, wherein said mammalian malignant cancer cell is in a human subject suffering from a malignant proliferative disease.

11. An inhibitory effective amount of at least one small molecule compound for use in a method for the inhibition and/or reduction of at least one metastatic property of a

cell, wherein said compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, and wherein said **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety;

wherein R is an imidazole derivative and/or triazine derivative;

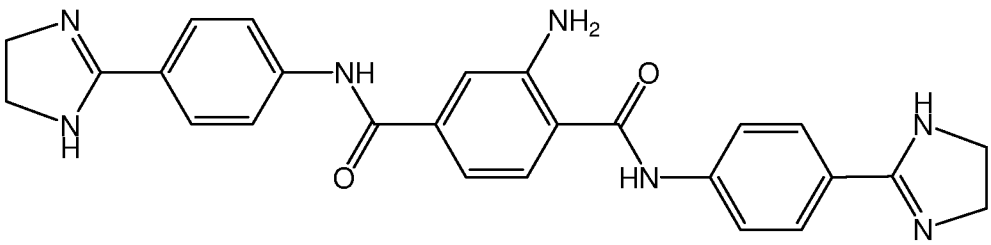
wherein each of said Ar and R may optionally be further substituted;

wherein n is an integer from 1 to 10; and

wherein when n>1, any one of said R may be the same or different.

12. The inhibitory effective amount of at least one small molecule compound for use according to claim 11, wherein said compound is at least one of:

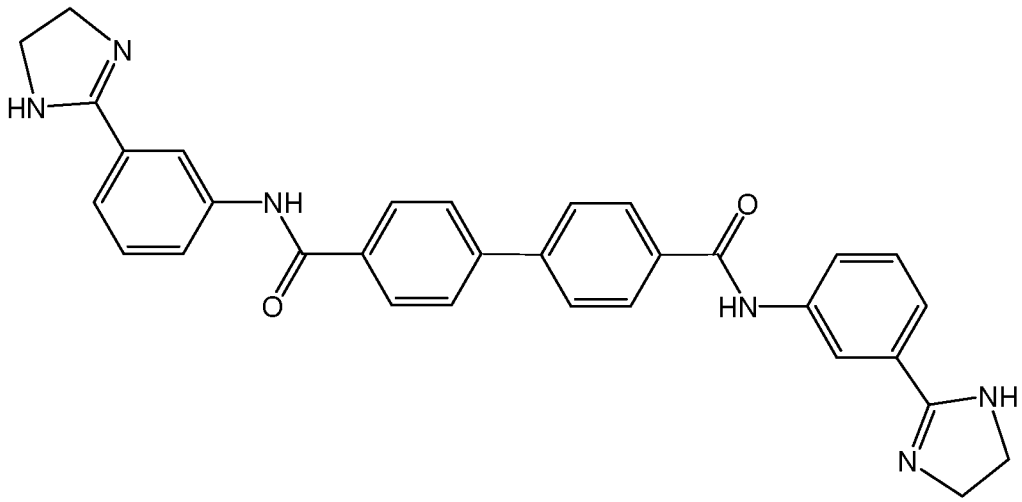
(a)



Formula III

a salt thereof, or any conjugates thereof;

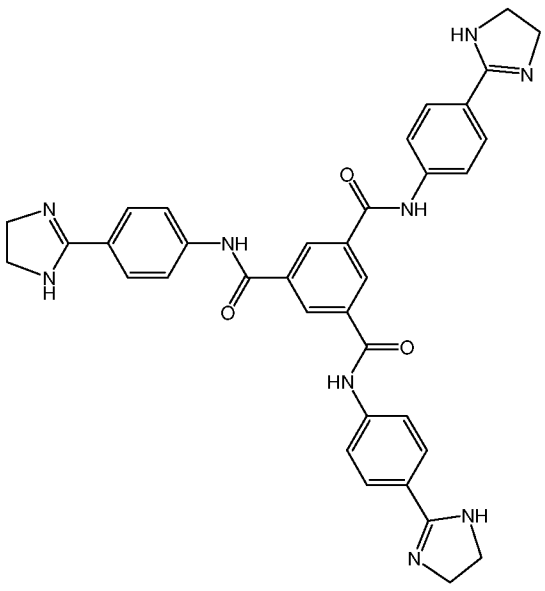
(b)



Formula IV

a salt thereof;

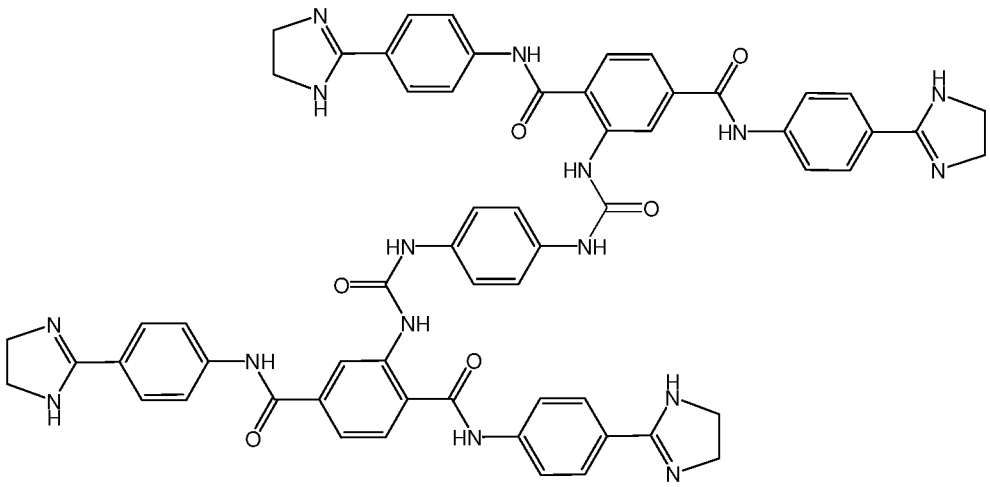
(c)



Formula V

a salt thereof;

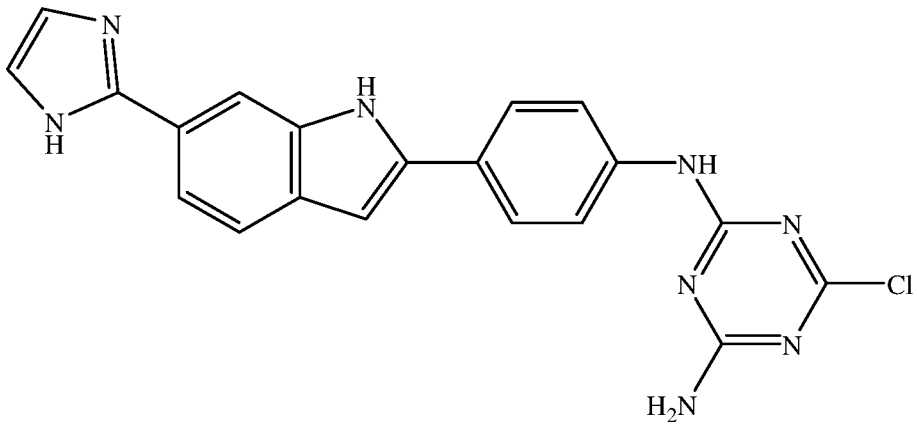
(d)



Formula VI

a salt thereof; and

(e)



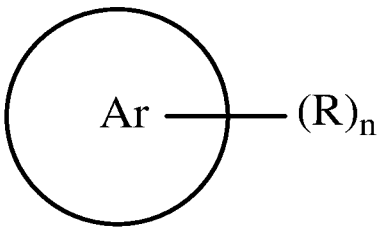
Formula VII

a salt thereof.

13. The inhibitory effective amount of at least one small molecule compound for use according to any one of claims 11 to 12, wherein said metastatic property of a cell is at least one of cell invasiveness, cell motility, cell migration and cell adhesion.

14. A method of inhibiting and/or reducing a metastatic process in a subject in need thereof, the method comprising the step of administering to said subject a

therapeutically effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof, or any composition thereof, wherein said **Formula I** is



Formula I

wherein Ar is an aromatic or heteroaromatic moiety;

wherein R is an imidazole derivative and/or triazine derivative;

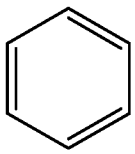
wherein each of said Ar and R may optionally be further substituted;

wherein n is an integer from 1 to 10; and

wherein when n>1, any one of said R may be the same or different.

15. The method according to claim 14, wherein Ar is selected from the group consisting of:

a)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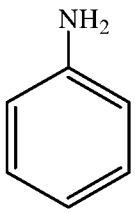
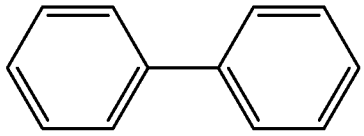
b)



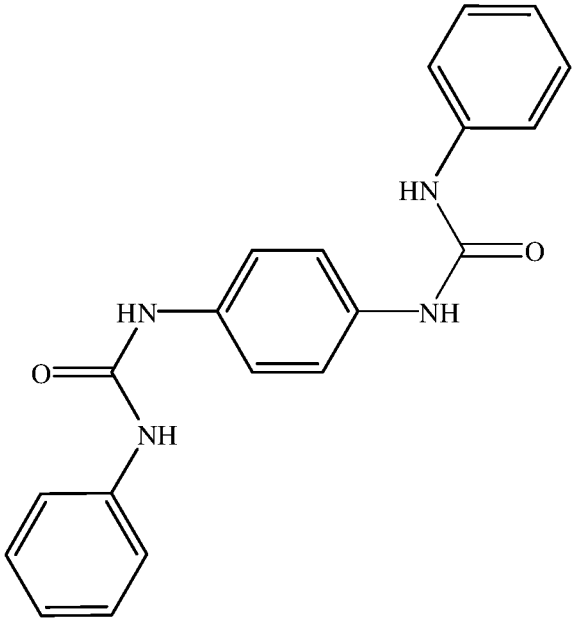
,

c)



, and

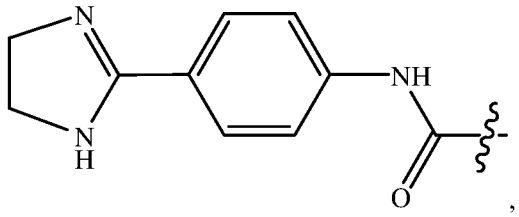
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

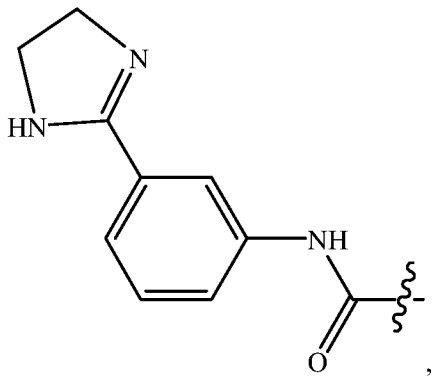
16. The method according to any one of claims 14 or 15, wherein R is selected from the group consisting of:

a)



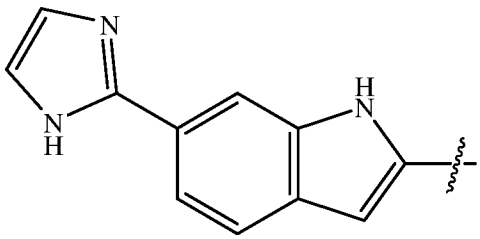
,

b)



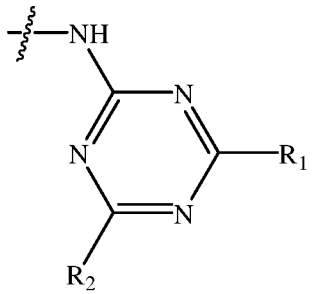
,

c)



, and

d)



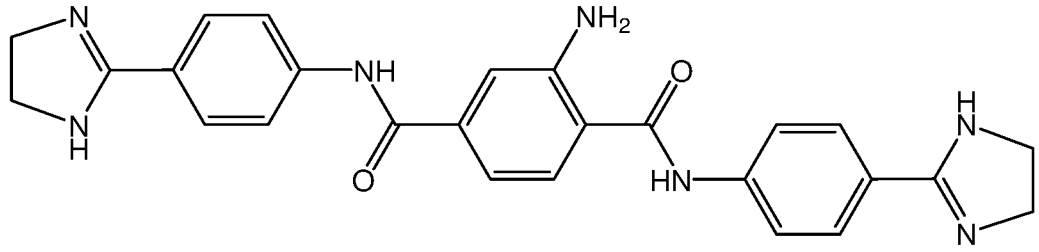
wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine, and wherein each of said R may optionally be further substituted.

17. The method according to any one of claims 14 to 16, wherein at least one of said R is an imidazole derivative.

18. The method according to any one of claims 14 to 17, wherein n is 2, 3, or 4.

19. The method according to any one of claims 14 to 18, wherein said compound is at least one of:

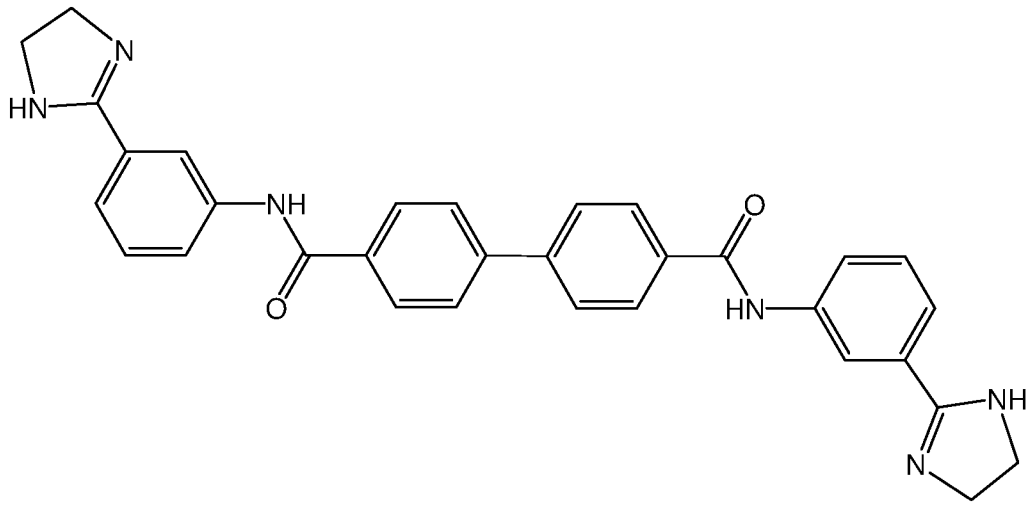
(a)



Formula III

a salt thereof, or any conjugates thereof;

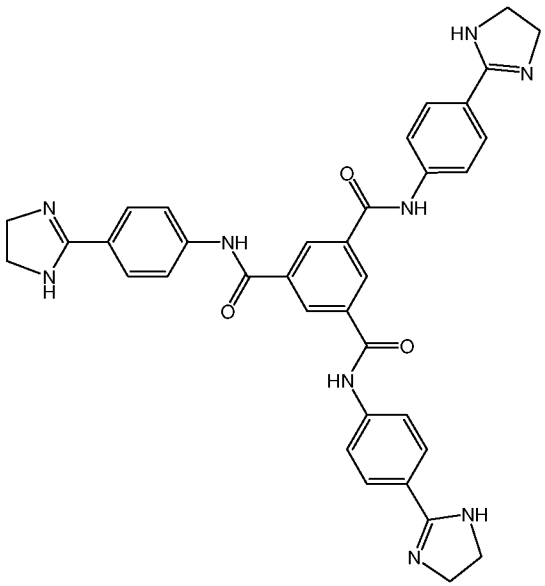
(b)



Formula IV

a salt thereof, or any conjugates thereof;

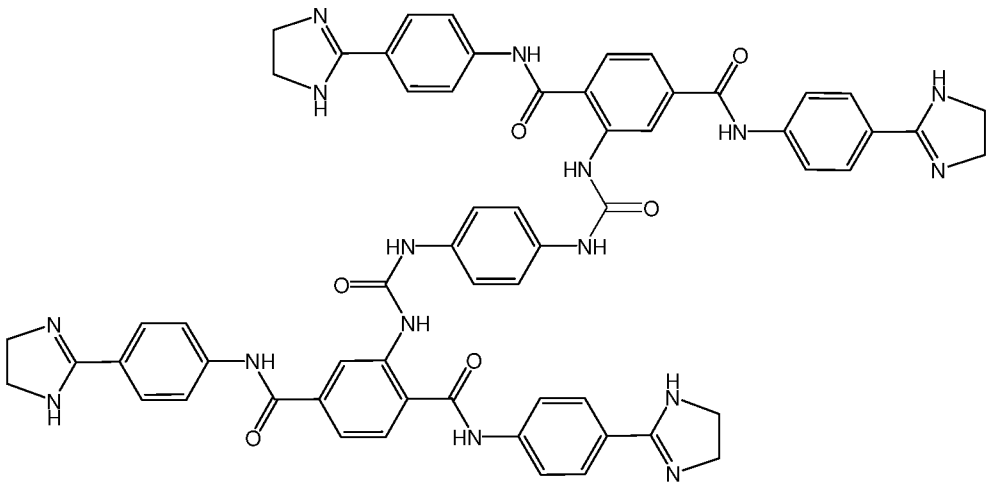
(c)



Formula V

a salt thereof, or any conjugates thereof;

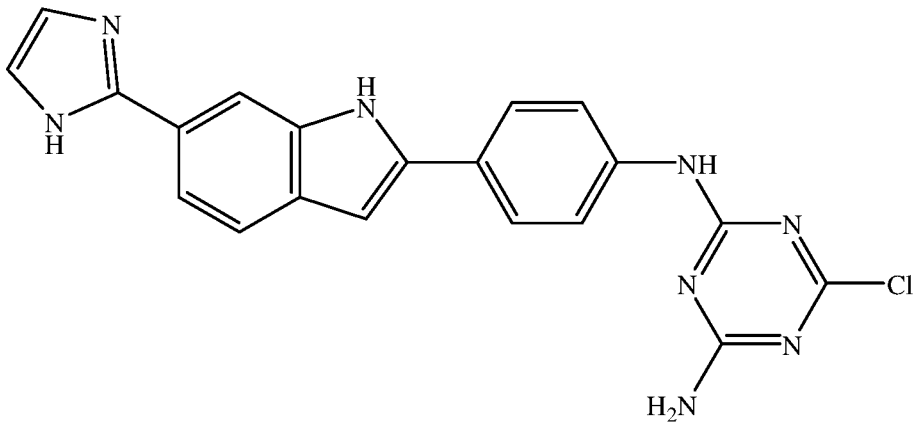
(d)



Formula VI

a salt thereof, or any conjugates thereof; and

(e)



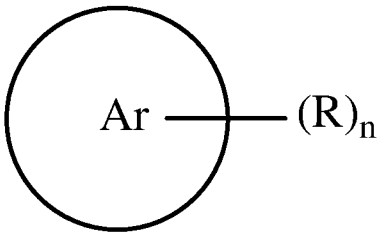
Formula VII

a salt thereof, or any conjugates thereof.

20. The method according to any one of claims 14 to 19, wherein the metastatic process is composed of a multi-step cascade comprising at least one of: tumor cell invasion, entry into a blood or lymph vessel system, transmigrating through the circulation and adhering to, and colonizing distal site/s.

21. The method according to any one of claims 14 to 20, wherein said subject is suffering of a proliferative malignant disease, said disease is at least one of breast cancer, bladder cancer, renal carcinoma, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, laryngeal cancer and hematopoietic malignancy.

22. An inhibitory effective amount of at least one small molecule compound for use in a method of inhibiting and/or reducing a metastatic process in a subject in need thereof, wherein said compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof of any compositions thereof, and wherein said **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety;

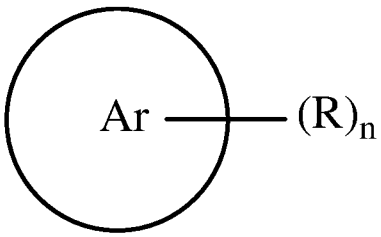
wherein R is an imidazole derivative and/or triazine derivative;

wherein each of said Ar and R may optionally be further substituted;

wherein n is an integer from 1 to 10; and

wherein when n>1, any one of said R may be the same or different.

23. A method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject, said method comprises the step of administering to said subject a therapeutically effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof, or any composition thereof, wherein said **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety;

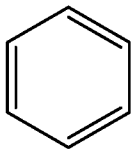
wherein R is an imidazole derivative and/or triazine derivative;

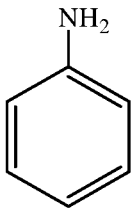
wherein each of said Ar and R may optionally be further substituted;

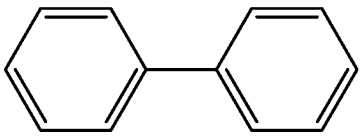
wherein n is an integer from 1 to 10; and

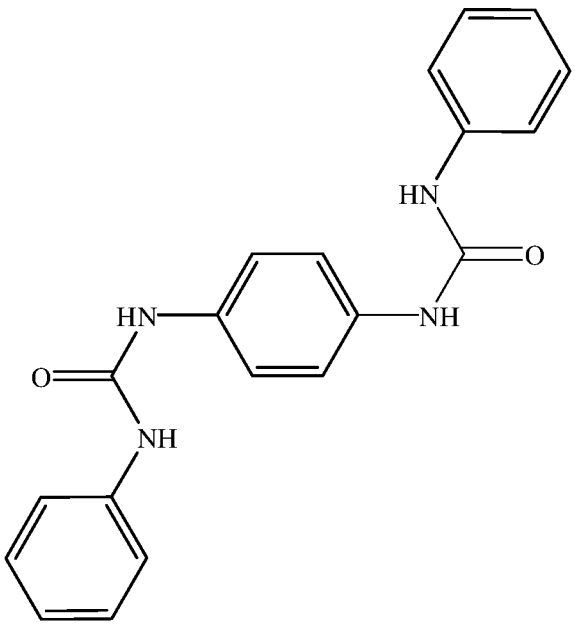
wherein when n>1, any one of said R may be the same or different.

24. The method according to claim 23, wherein Ar is selected from the group consisting of:

a) ,

b) ,

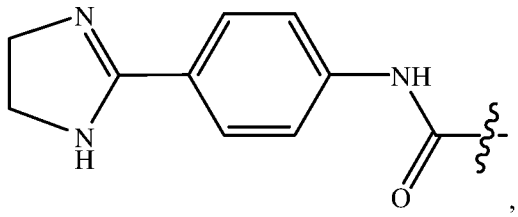
c) , and

d) 

wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

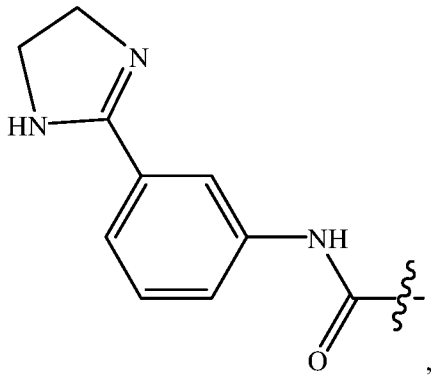
25. The method according to any one of claims 23 or 24, wherein R is selected from the group consisting of:

a)



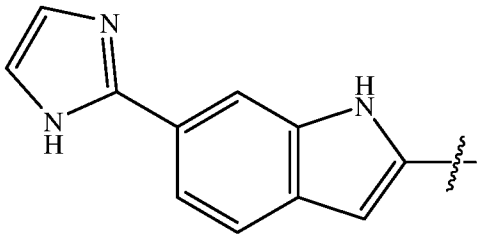
,

b)



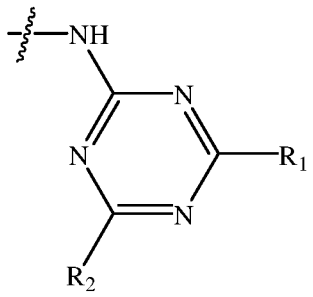
,

c)



, and

d)



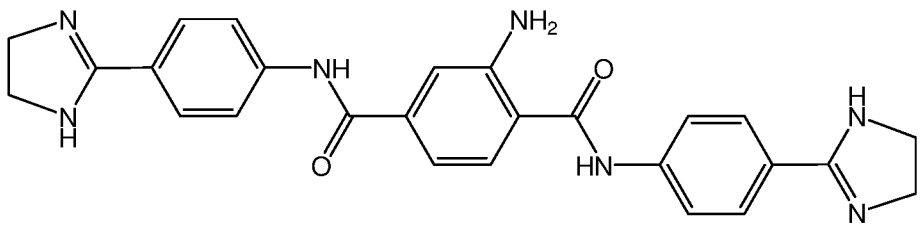
wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine and wherein each of said R may optionally be further substituted.

26. The method according to any one of claims 23 to 25, wherein at least one of the said R is an imidazole derivative.

27. The method according to any one of claims 23 to 26, wherein n is 2, 3, or 4.

28. The method according to any one of claims 23 to 27, wherein said compound is at least one of:

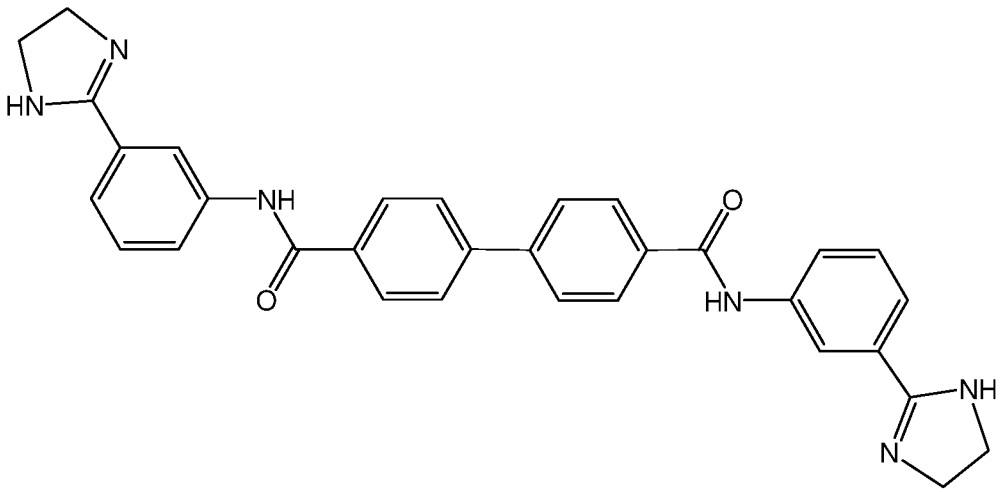
(a)



Formula III

a salt thereof, or any conjugates thereof;

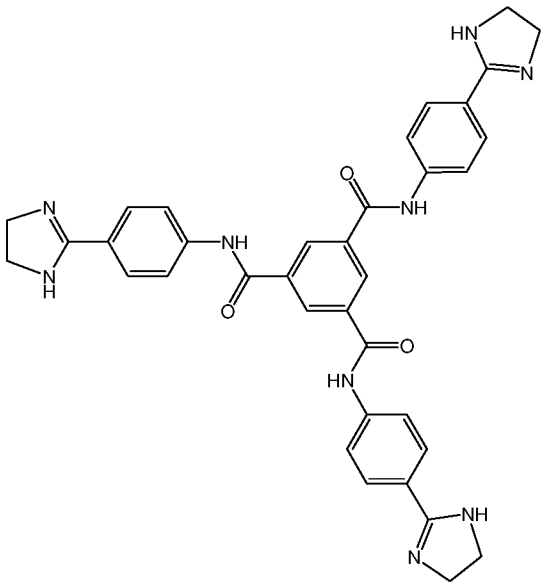
(b)



Formula IV

a salt thereof, or any conjugates thereof;

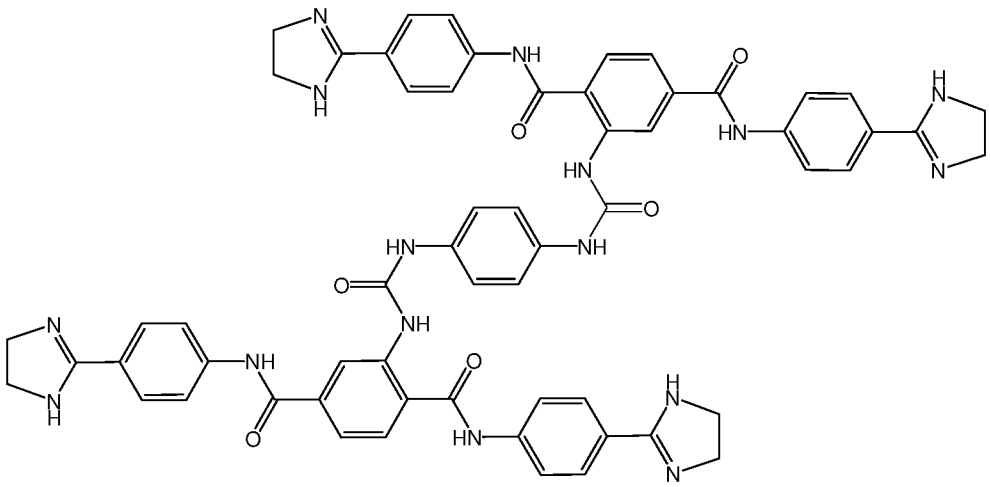
(c)



Formula V

a salt thereof, or any conjugates thereof;

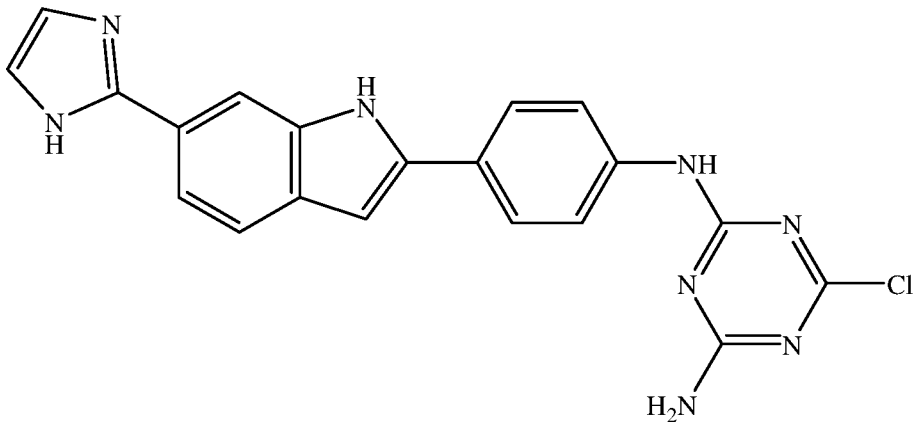
(d)



Formula VI

a salt thereof or any conjugates thereof; and

(e)



Formula VII

a salt thereof or any conjugates thereof.

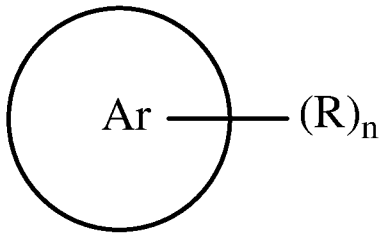
29. The method according to any one of claims 23 to 28, wherein said proliferative malignant disease is at least one of breast cancer, bladder cancer, kidney cancer, hepatocellular carcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy

30. The method according to any one of claims 23 to 29, wherein said proliferative malignant disease is a metastatic disease originated from a primary and/or secondary proliferative malignant disease, said proliferative malignant disease is at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

31. The method according to any one of claims 23 to 30, wherein said primary proliferative malignant disease exists in a dormant, inactive state.

32. The method according to any one claims 23 to 31, wherein said subject is further treated with at least one anti-proliferative compound and/or procedure, prior to, after, and/or simultaneously with the administration of said at least one small molecule compound.

33. An inhibitory effective amount of at least one small molecule compound for use in a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject, wherein said compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, and wherein said **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety;

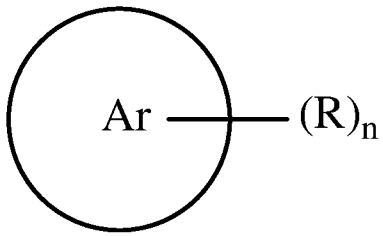
wherein R is an imidazole derivative and/or triazine derivative;

wherein each of said Ar and R may optionally be further substituted;

wherein n is an integer from 1 to 10; and

wherein when n>1, any one of said R may be the same or different.

34. A method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject treated with at least one anti-proliferative compound and/or procedure, said method comprises the step of administering to said subject a therapeutically effective amount of at least one small molecule compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof, or any composition thereof, prior to, after, and/or simultaneously with said at least one anti-proliferative compound and/or procedure, wherein said **Formula I** is:



Formula I

wherein Ar is an aromatic or heteroaromatic moiety;

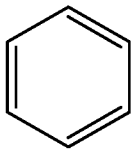
wherein R is an imidazole derivative and/or triazine derivative;

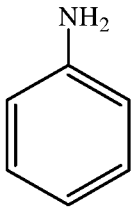
wherein each of said Ar and R may optionally be further substituted;

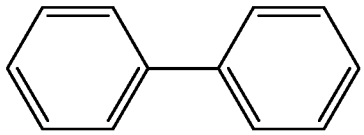
wherein n is an integer from 1 to 10; and

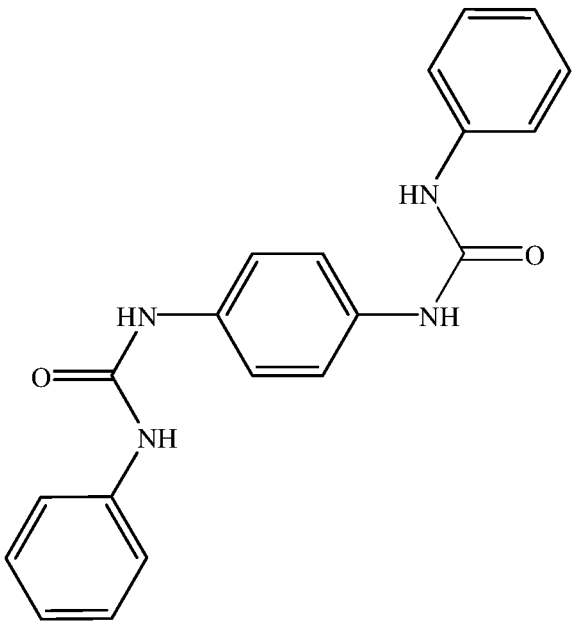
wherein when n>1, any one of said R may be the same or different.

35. The method according to claim 34, wherein Ar is selected from the group consisting of:

a) ,

b) ,

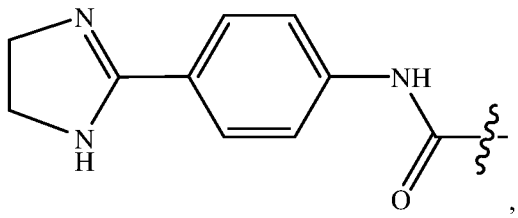
c) , and

d) 

wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R and wherein each of said Ar may optionally be further substituted.

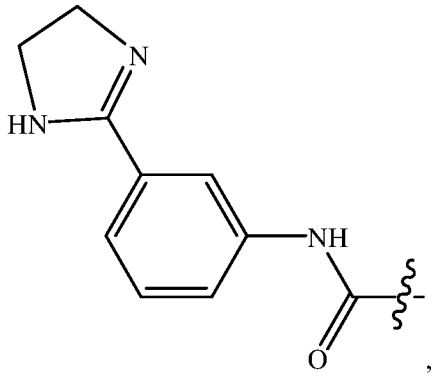
36. The method according to any one of claims 34 or 35, wherein R is selected from the group consisting of:

a)



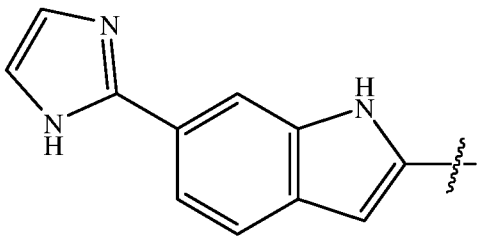
,

b)



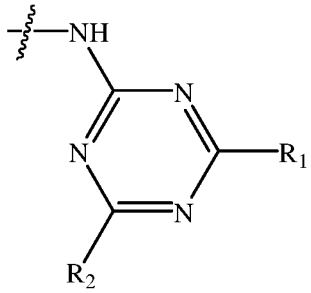
,

c)



, and

d)



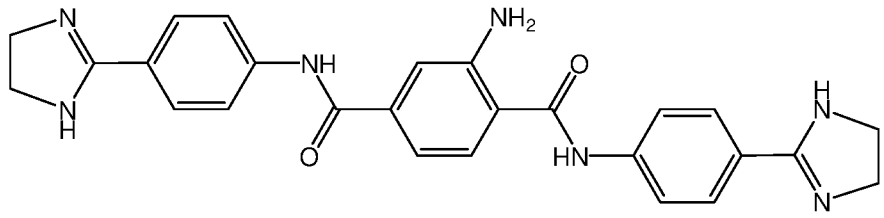
wherein R_1 and R_2 each are independently selected from the group consisting of hydrogen, halogen, -OH, -NH_2, straight or branched C_{1-5} alkyl, straight or branched C_{1-5} alkoxy, and straight or branched C_{1-5} amine, and wherein each of said R may optionally be further substituted.

37. The method according to any one of claims 34 to 36, wherein at least one of the said R is an imidazole derivative.

38. The method according to any one of claims 34 to 37, wherein n is 2, 3, or 4.

39. The method according to any one of claims 34 to 38, wherein said compound is at least one of:

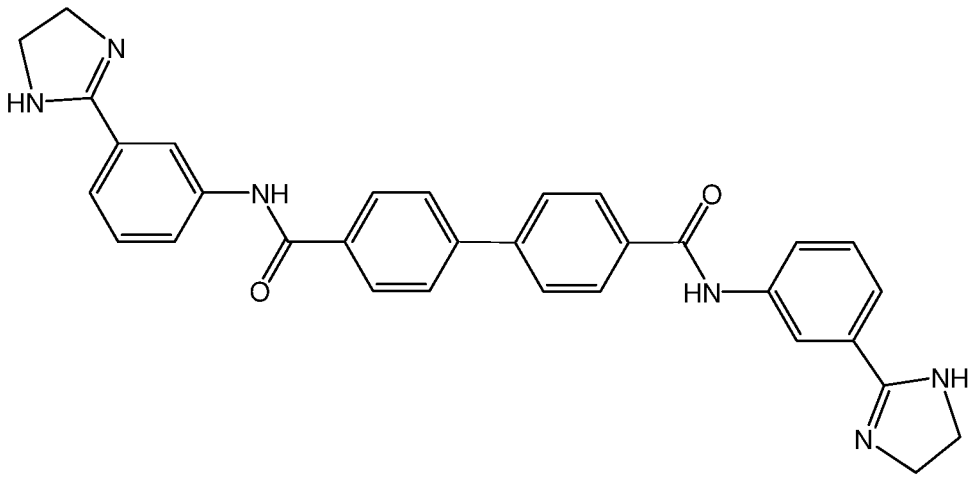
(a)



Formula III

a salt thereof or any conjugates thereof;

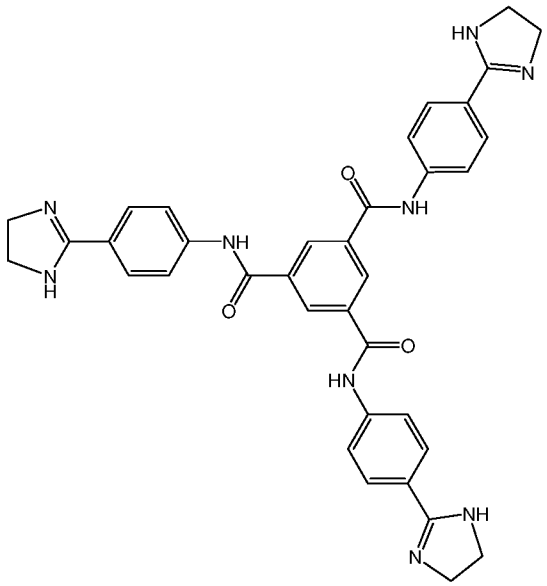
(b)



Formula IV

a salt thereof or any conjugates thereof;

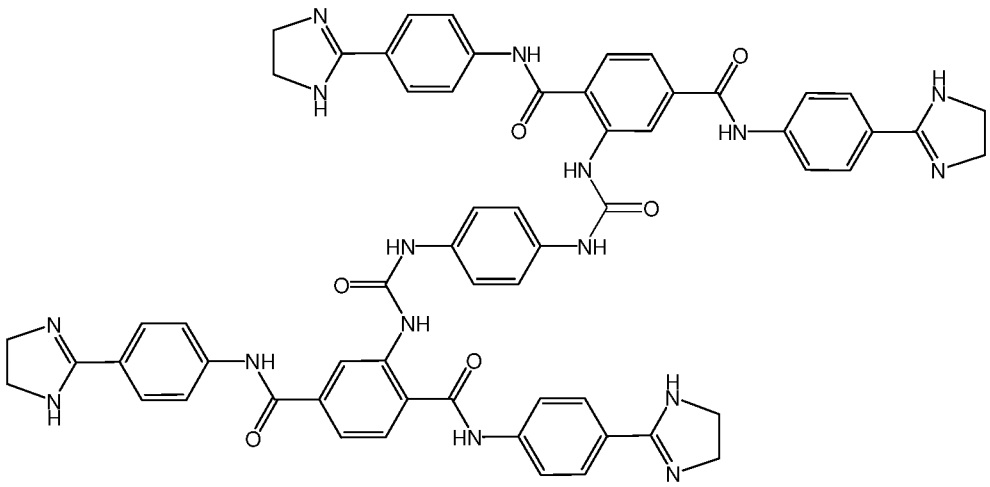
(c)



Formula V

a salt thereof, or any conjugates thereof;

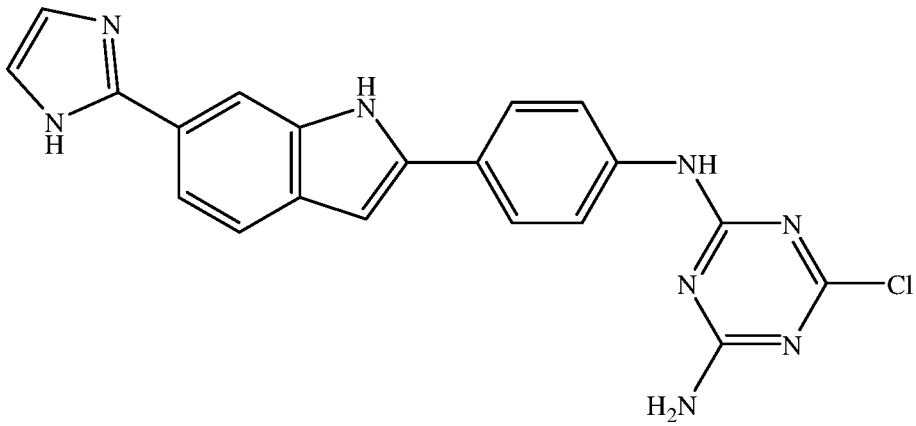
(d)



Formula VI

a salt thereof, and

(e)



Formula VII

a salt thereof or any conjugates thereof.

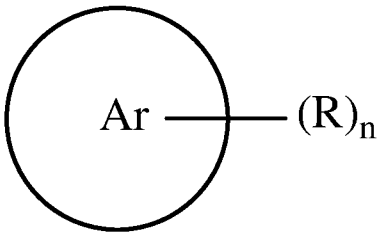
40. The method according to any one of claims 34 to 39, wherein said anti-proliferative compound and/or procedure may comprise at least one of chemotherapy, radiosurgery, radiation therapy, biological therapy, immune-therapy, hormone therapy, surgery, or any combination thereof.

41. The method according to any one of claims 34 to 40, wherein said proliferative malignant disease is at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

42. The method according to any one of claims 34 to 41, wherein said proliferative malignant disease is a metastatic disease originated from a primary and/or secondary proliferative malignant disease, said proliferative malignant disease is at least one of breast cancer, bladder cancer, kidney cancer, hepatocarcinoma cancer, pancreatic cancer, colorectal cancer, gastric cancer, non-small cell lung cancer, melanoma, osteosarcoma, ovarian cancer, prostate cancer, thyroid cancer, cervical cancer, uterus cancer, laryngeal cancer and hematopoietic malignancy.

43. The method according to any one of claims 34 to 42, wherein said primary proliferative malignant disease exists in a dormant, inactive state.

44. An inhibitory effective amount of at least one small molecule compound for use in a method for treating, preventing, inhibiting, reducing, eliminating, protecting, ameliorating, or delaying the onset of a proliferative malignant disease in a subject treated with at least one anti-proliferative compound and/or procedure, wherein said compound is a compound of **Formula I**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any compositions thereof, and wherein said **Formula I** is:

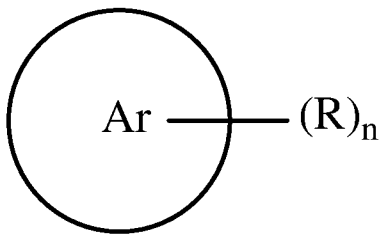


Formula I

wherein Ar is an aromatic or heteroaromatic moiety;

wherein R is an imidazole derivative and/or triazine derivative;
wherein each of said Ar and R may optionally be further substituted;
wherein n is an integer from 1 to 10; and
wherein when n>1, any one of said R may be the same or different.

45. A method for modulating the activity, of at least one antisense long non-coding RNA of the metastasis suppressor gene KAI1/cluster of differentiation 82 (CD82) (KAI1 as-lncRNA, suppressor of KAI1 in breast cancer (SKAIBC), in a cell, the method comprising the step of contacting said cell with a modulatory effective amount of at least one small molecule compound of **Formula II**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or with any vehicle, matrix, nano-, micro-particles thereof, any combinations thereof or any composition thereof, wherein said **Formula II** is:

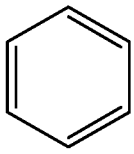


Formula II

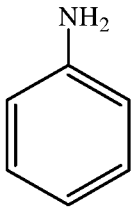
wherein Ar is an aromatic or heteroaromatic moiety;
wherein R is a dihydroimidazole derivative;
wherein each of said Ar and R may optionally be further substituted;
wherein n is an integer from 1 to 10;
wherein when n>1, any one of said R may be the same or different, and wherein said KAI1 as-lncRNA has a length of about 700 to about 1000 nucleotides and is encoded upstream of the KAI1/CD82 gene transcription start site (TSS) in an antisense orientation.

46. The method according to claim 45, wherein Ar is selected from the group consisting of:

a)


,

b)



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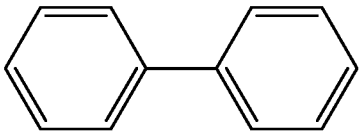
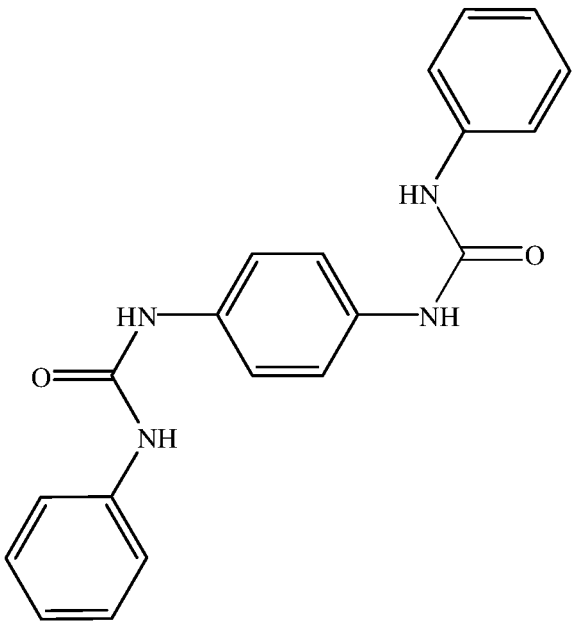
c)


, and

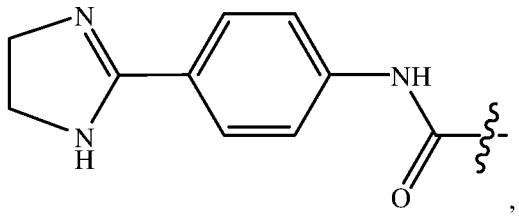
d)



wherein in any one of said Ar, each of the phenyl rings may be independently substituted with one or more of said R, and wherein each of said Ar may optionally be further substituted.

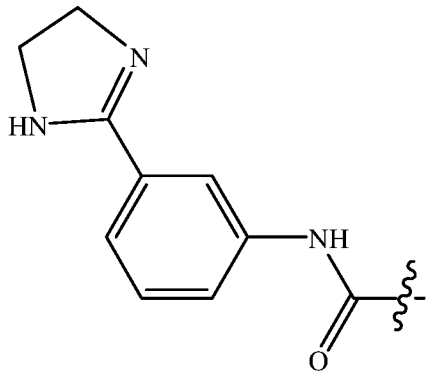
47. The method according to any one of claims 45 or 46, wherein R is selected from the group consisting of:

a)



,

b)

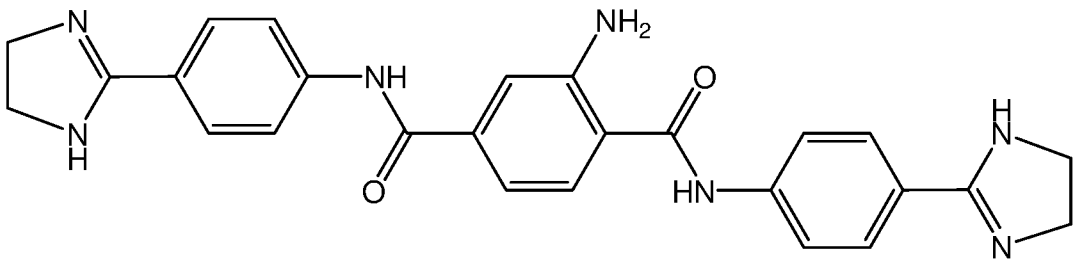


and wherein each of said R may optionally be further substituted.

48. The method according to any one of claims 45 to 47, wherein n is 2, 3, or 4.

49. The method according to any one of claims 45 to 48, wherein said compound is at least one of:

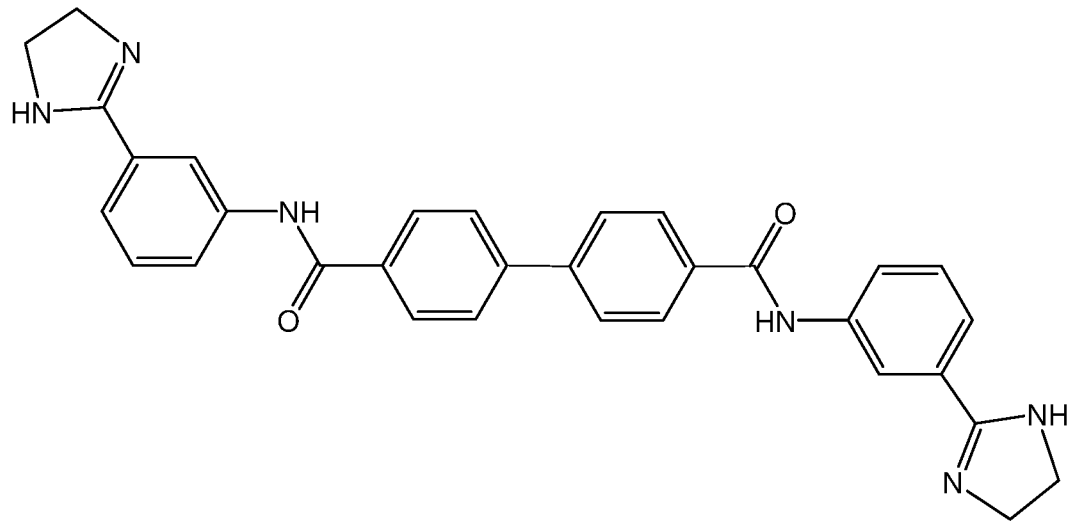
(a)



Formula III

a salt thereof or any conjugates thereof;

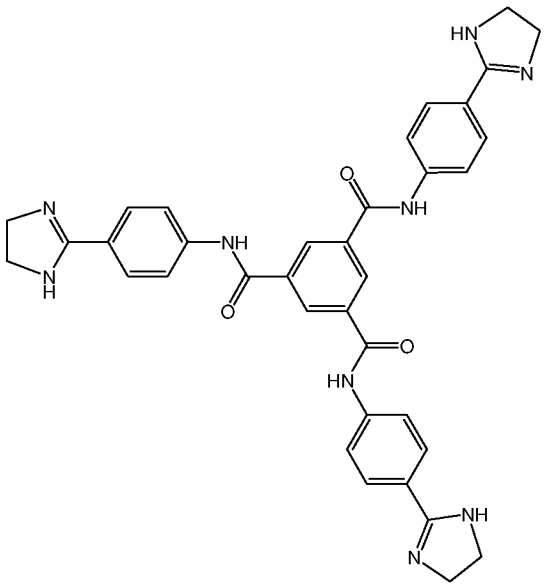
(b)



Formula IV

a salt thereof or any conjugates thereof;

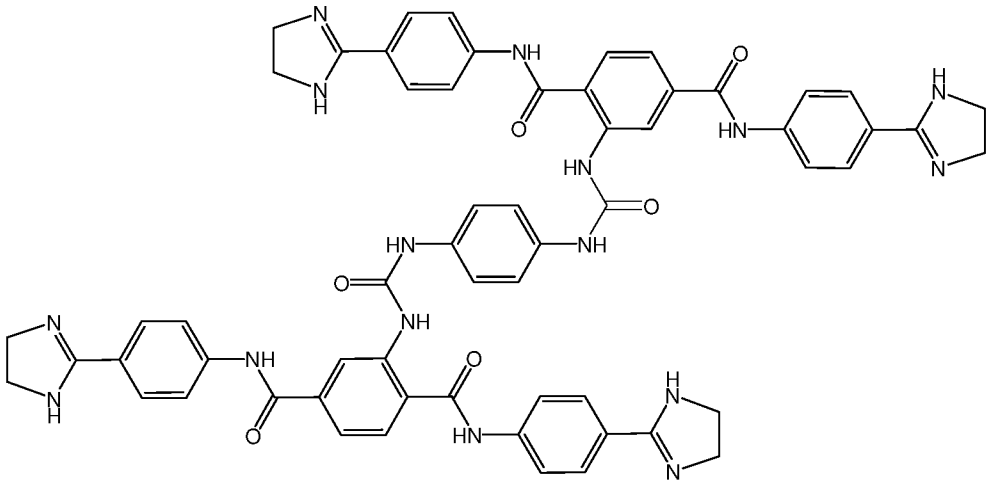
(c)



Formula V

a salt thereof or any conjugates thereof ; and

(d)



Formula VI

a salt thereof or any conjugates thereof.

50. The method according to any one of claims 45 to 49, wherein said small molecule compound of Formula II, reduces the activity of the KAI1 as-lncRNA transcript, thereby increasing the expression of the KAI1/CD82 gene.

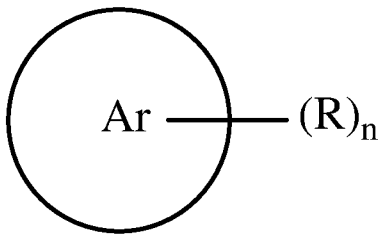
51. The method according to any one of claims 45 to 50, wherein said method results in the inhibition of at least one metastatic property of said cell.

52. The method according to any of claims 45 to 51, wherein said metastatic property is at least one of cell invasiveness, cell motility, cell migration and cell adhesion.

53. The method according to any of claims 45 to 52, wherein said cell is a mammalian malignant cancer cell.

54. The method according to any of claims 45 to 53, wherein said mammalian malignant cancer cell is of a primary and/or secondary origin of at least one of breast tissue, bladder tissue, kidney tissue, hepatic tissue, pancreatic tissue, colorectal tissue, gastric tissue, lung tissue, skin tissue, ovarian tissue, prostate tissue, thyroid tissue, cervical tissue, endometrium tissue, laryngeal tissue, bone tissue and hematopoietic tissue.

55. At least one small molecule compound of **Formula II**, a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, any conjugates thereof, or any vehicle, matrix, nano-, micro-particles thereof, for use in a method for modulating the levels and/or stability of at least one antisense long non-coding RNA of the metastasis suppressor gene KAI1/cluster of differentiation 82 (CD82) (KAI1 as-lncRNA, suppressor of KAI1 in breast cancer (SKAIBC)), in a cell, wherein said Formula II is:



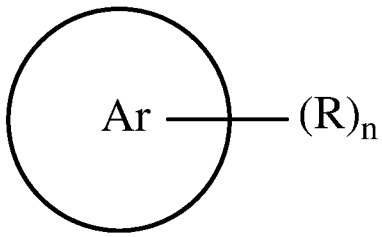
Formula II

wherein Ar is an aromatic or heteroaromatic moiety;

wherein R is a dihydroimidazole derivative;

wherein each of said Ar and R may optionally be further substituted;
wherein n is an integer from 1 to 10; wherein when n>1, any one of said R may be the same or different, and wherein said KAI1 as-lncRNA has a length of about 700 to about 1000 nucleotides and is encoded upstream of the KAI1/CD82 gene transcription start site (TSS) in an antisense orientation, and wherein said KAI1 as-lncRNA has a length of about 700 to about 1000 nucleotides and is encoded upstream of the KAI1/CD82 gene transcription start site (TSS) in an antisense orientation.

56. A compound of general **Formula I**



Formula I,

a pharmaceutically acceptable salt, solvate, hydrate or isomer thereof, or with any vehicle, matrix, nano-, micro-particles thereof,
wherein Ar is an aromatic or heteroaromatic moiety;
wherein R is an imidazole derivative and/or triazine derivative;
wherein each of said Ar and R may optionally be independently further substituted;
wherein n is an integer from 1 to 10; and
wherein when n>1, any one of the R may be the same or different,
provided that said compound of **Formula I** is not any one of the compounds of Formulas IV, III, V, VI, VIII and VII disclosed herein.

57. A composition comprising the compound of claim 56, the composition optionally further comprises at least one pharmaceutically acceptable carrier/s, excipient/s, auxiliaries, and/or diluent/s.

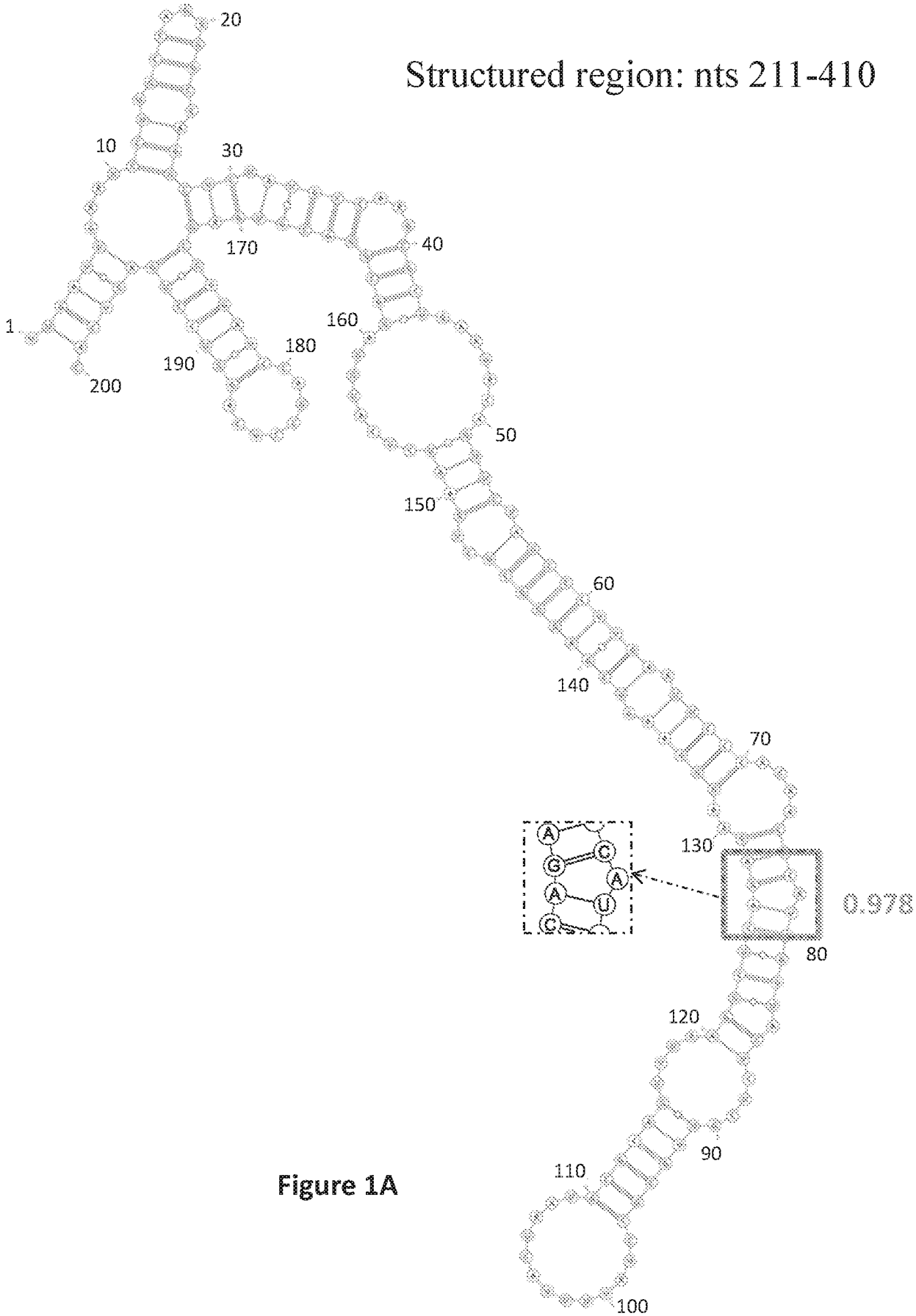

Structured region: nts 211-410
20
10
30
170
40
1
160
180
190
200
50
150
60
140
70
130
0.978
80
120
90
110
100

Figure 1A

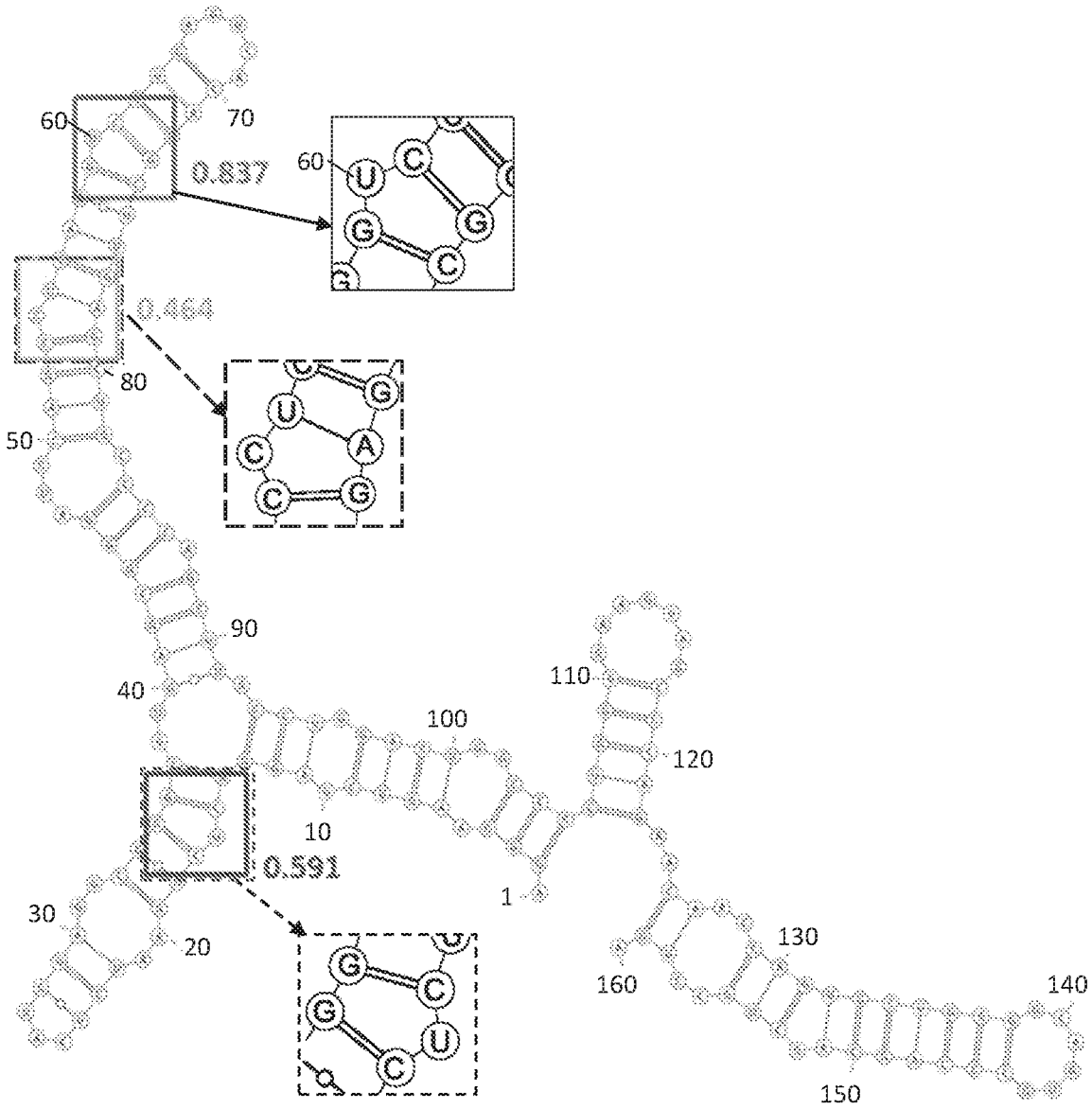

Structured region: nts 341-500
60
70
0.837
60
U
C
G
G
C
0.464
80
50
G
U
C
A
C
G
90
40
110
100
120
10
0.591
1
30
20
130
160
140
150
G
C
G
U
C

Figure 1B

Structured region: nts 381-640

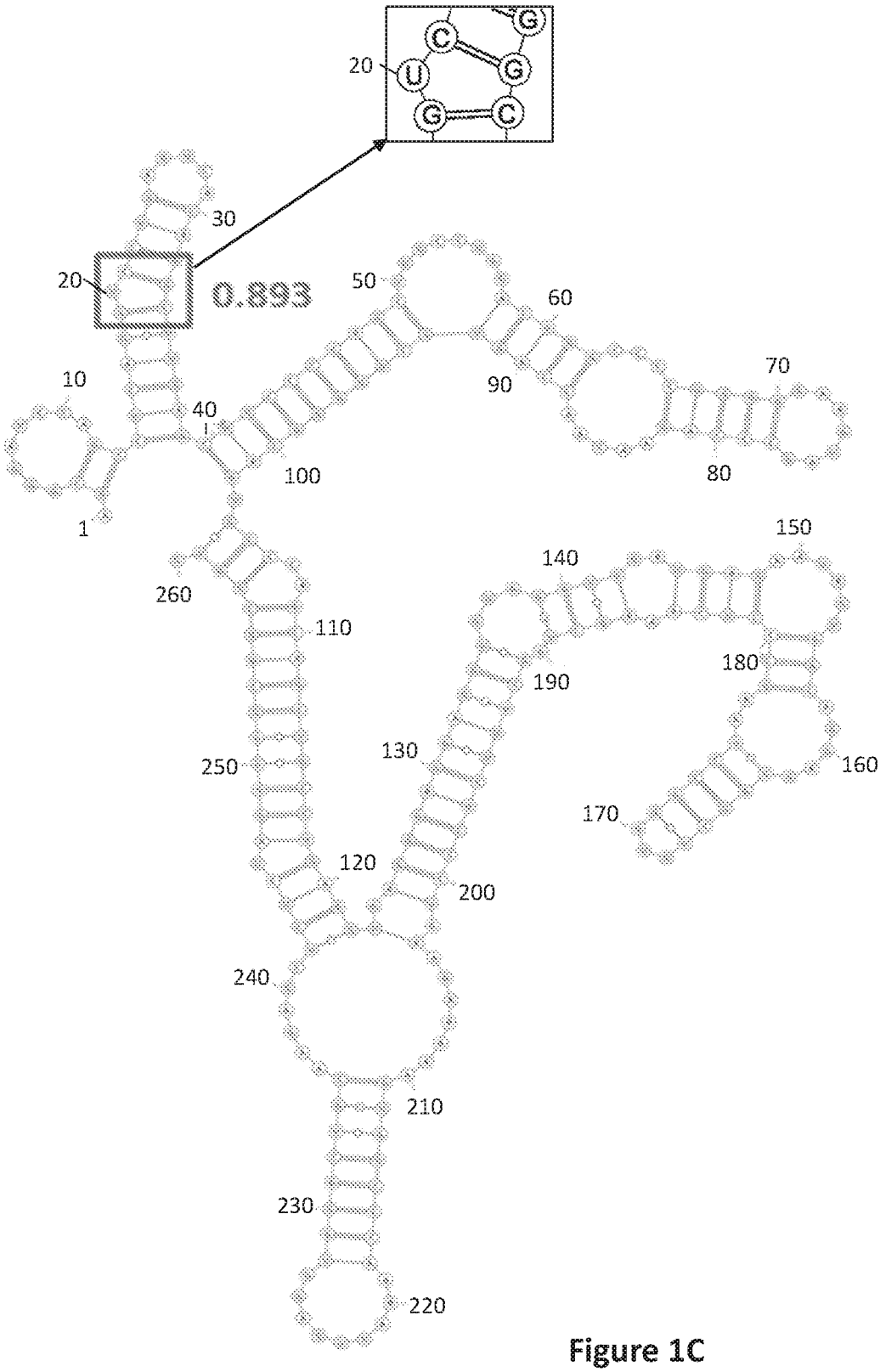


Figure 1C

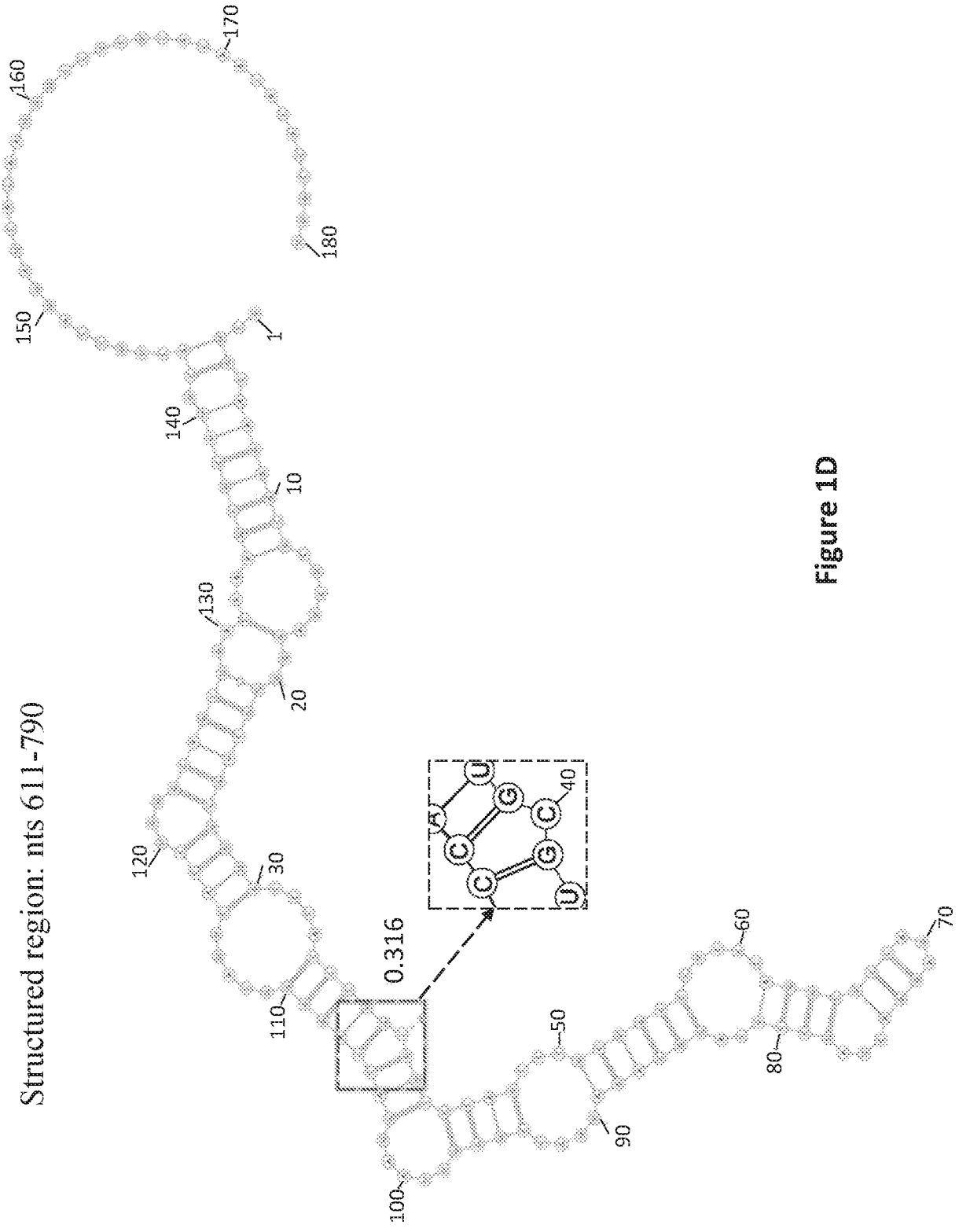

Structured region: nts 611-790
0.316
A
U
G
C
C
G
C
U
1
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

Figure 1D

Figure 2A

Structured region: nts 211-410

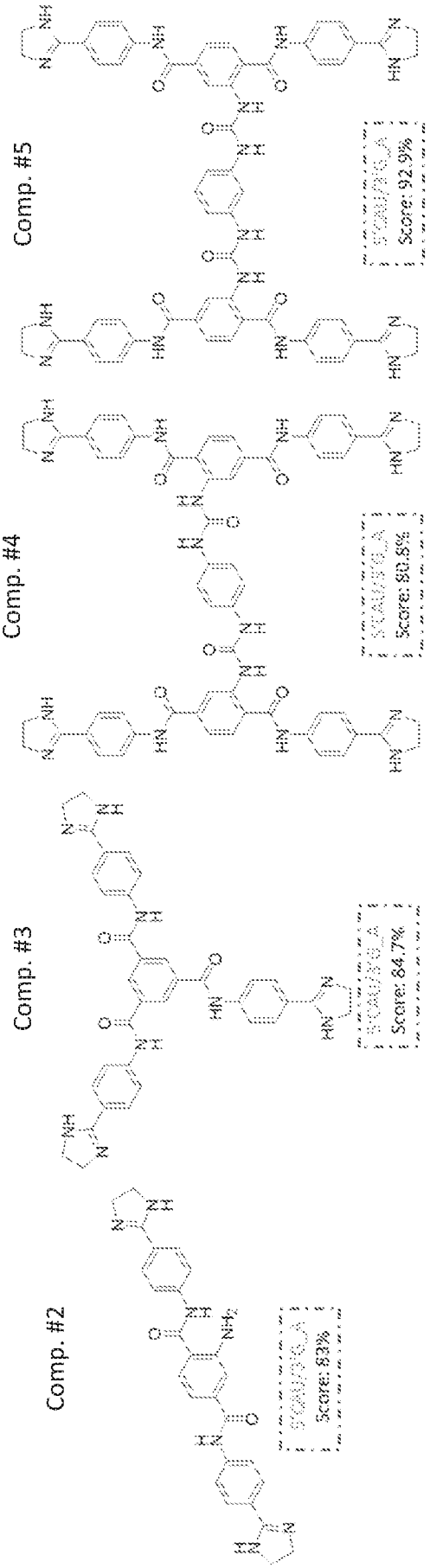


Figure 2B Structured region: nts 341-500

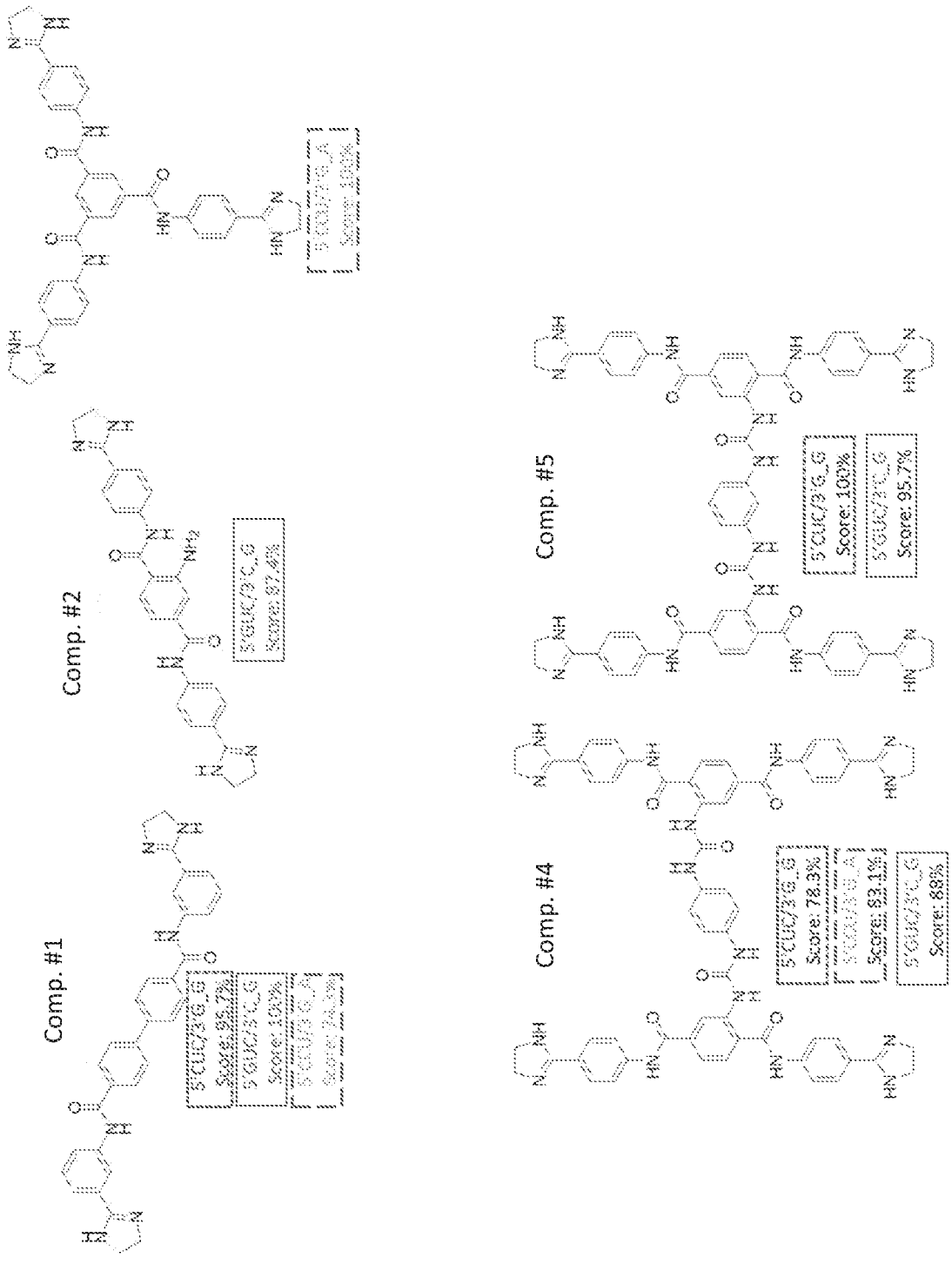


Figure 2C Structured region: nts 381-640

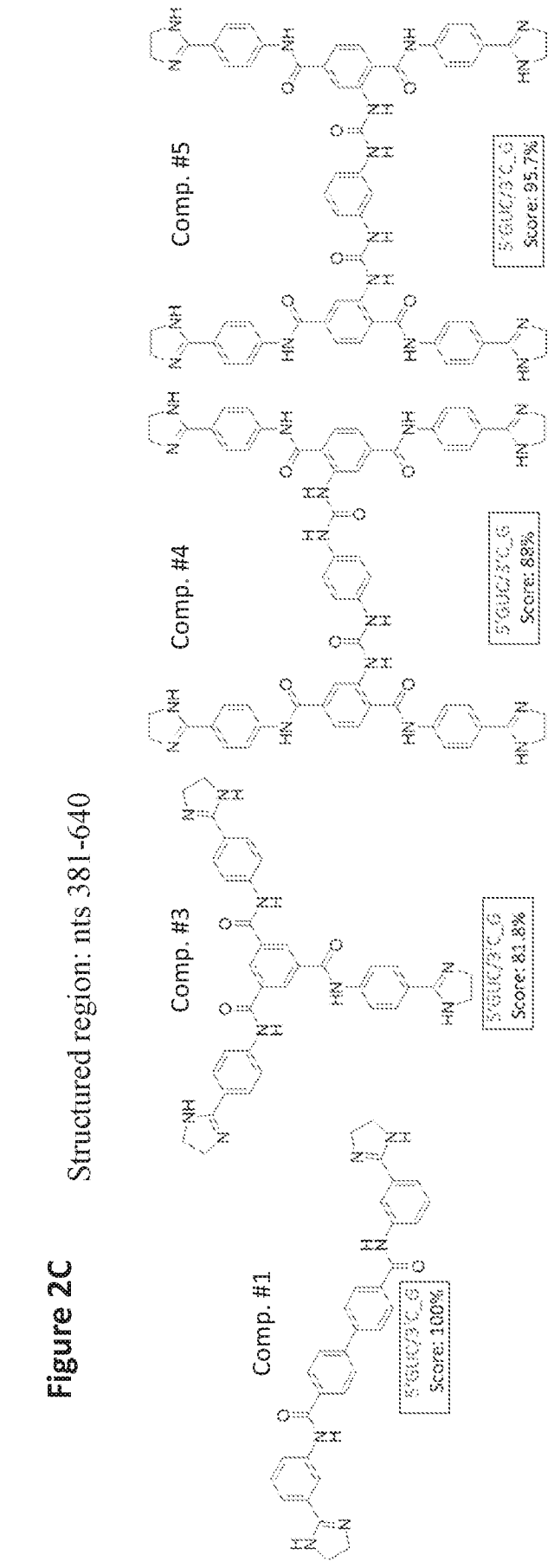
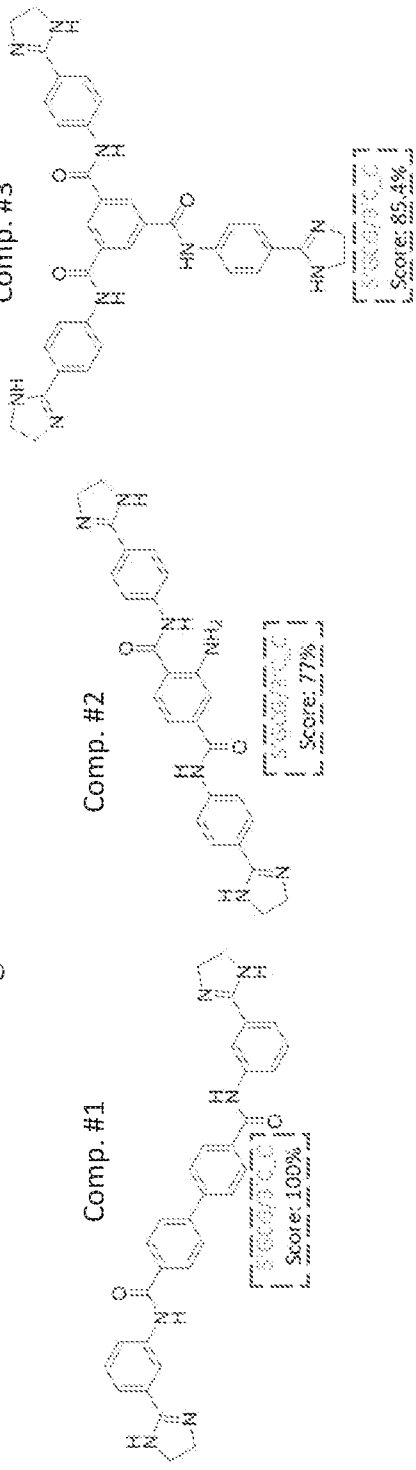


Figure 2D Structured region: nts 611-790



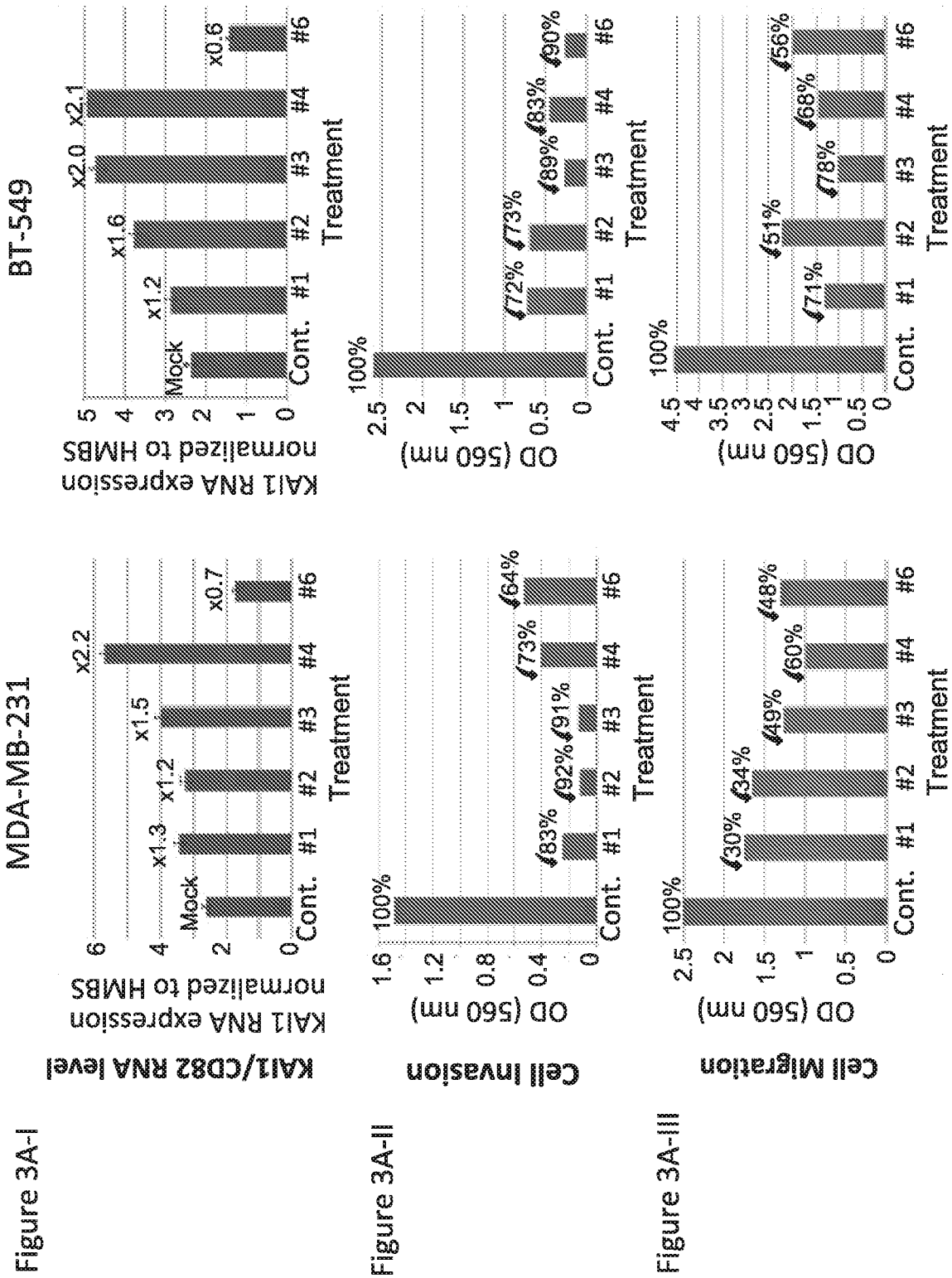


Figure 3A-I

Figure 3A-II

Figure 3A-III

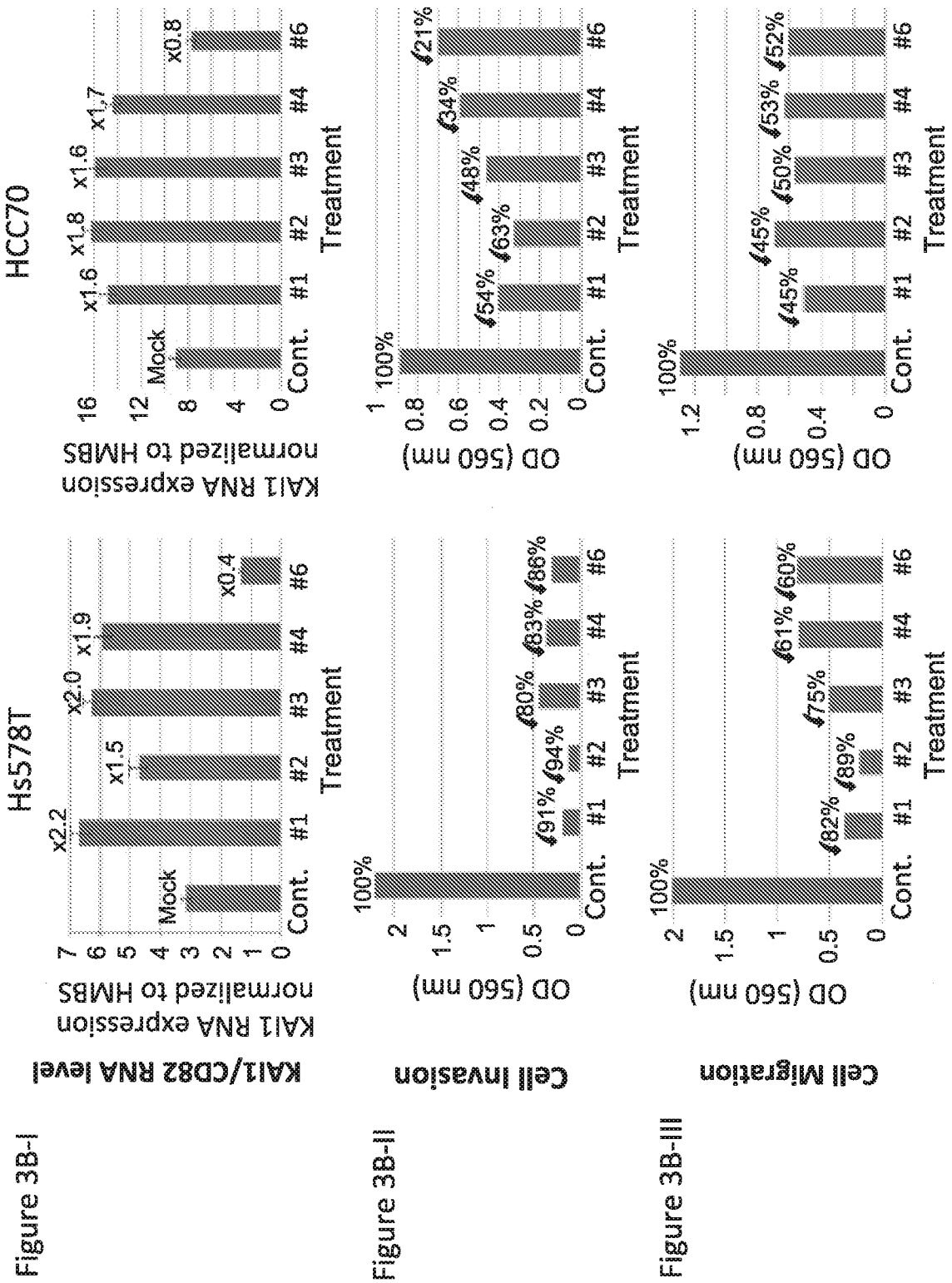


Figure 3B-I
KAI1/CD82 RNA level
Hs578T
KAI1 RNA expression normalized to HMBS
Mock
x2.2
x1.5
x2.0
x1.9
x0.4
Cont.
#1
#2
#3
#4
#6
Treatment
HCC70
KAI1 RNA expression normalized to HMBS
Mock
x1.6
x1.8
x1.6
x1.7
x0.8
Cont.
#1
#2
#3
#4
#6
Treatment
Figure 3B-II
Cell invasion
OD (560 nm)
100%
91%
94%
80%
83%
86%
Cont.
#1
#2
#3
#4
#6
Treatment
OD (560 nm)
100%
54%
63%
48%
34%
21%
Cont.
#1
#2
#3
#4
#6
Treatment
Figure 3B-III
Cell Migration
OD (560 nm)
100%
82%
89%
75%
61%
60%
Cont.
#1
#2
#3
#4
#6
Treatment
OD (560 nm)
100%
45%
45%
50%
53%
52%
Cont.
#1
#2
#3
#4
#6
Treatment

Figure 4-I
MCF-7 (Luminal A)
ZR-75-30 (Luminal B)
SkBr3 (HER2+)
KAI1/CD82 RNA level
KAI1 RNA expression normalized to HMBS
Mock
x1.1
x1.2
x1.1
x0.5
x0.7
x0.70
x0.92
x1.03
x1.08
x0.86
x0.6
x0.9
x1.0
x1.0
x1.1
Cont.
#1
#2
#3
#4
#6
Treatment
Figure 4-II
Cell invasion
OD (560 nm)
100%
52%
66%
80%
75%
67%
58%
84%
65%
64%
42%
74%
84%
85%
83%
83%
Figure 4-III
Cell Migration
OD (560 nm)
100%
76%
73%
64%
58%
67%
60%
88%
42%
75%
22%
62%
74%
39%
64%
85%

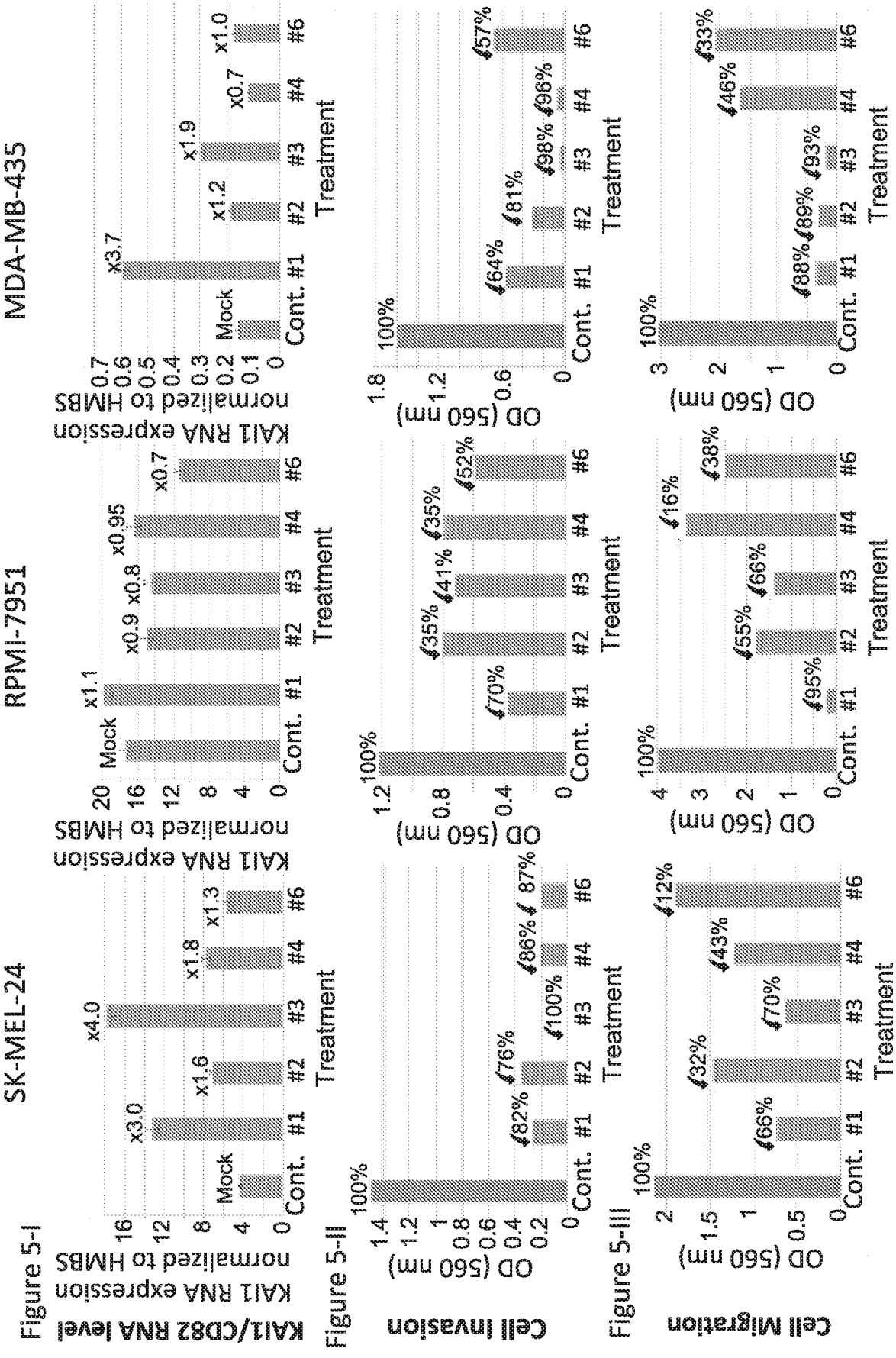


Figure 5-I
SK-MEL-24
RPMI-7951
MDA-MB-435
KAI1/CD82 RNA level
KAI1 RNA expression
normalized to HMBS
Mock
Cont.
#1
#2
#3
#4
#6
x4.0
x3.0
x1.6
x1.8
x1.3
x1.1
x0.9
x0.8
x0.95
x0.7
x3.7
x1.2
x1.9
x0.7
x1.0
Treatment
Figure 5-II
Cell Invasion
OD (560 nm)
100%
82%
76%
100%
86%
87%
70%
35%
41%
35%
52%
64%
81%
98%
96%
57%
95%
55%
66%
16%
38%
88%
89%
93%
Figure 5-III
Cell Migration
66%
32%
70%
43%
12%
46%
33%

AsPC-1
BxPC-3
CFPAC-1
KAI1/CD82 RNA level
KAI1 RNA expression normalized to HMBS
Mock
x2.5
x1.3
x1.6
x1.2
x3.6
x2.2
x1.3
x1.9
x1.5
x1.3
Mock
x1.1
x1.0
x1.5
x1.6
x1.9
Cont.
#1
#2
#3
#4
#6
Treatment
Figure 6-I
Figure 6-II
Figure 6-III
Cell invasion
Cell Migration
OD (560 nm)
100%
84%
76%
77%
77%
79%
91%
92%
94%
94%
93%
58%
23%
61%
48%
47%
47%
61%
25%
47%
33%
74%
82%
76%
77%
84%
46%
83%
83%
57%
47%

Figure 7A-I

Figure 7A-II

Figure 7A-III

Figure 7B-I

KAI1/CD82 RNA level

Figure 7B-II

Cell Invasion

Figure 7B-III

Cell Migration

Figure 8-I
KAI1/CD82 RNA level
SK-HEP1
KAI1 RNA expression normalized to HMBS
Mock
x1.0
x1.1
x1.1
x1.7
x0.8
Control
#1
#2
#3
#4
#6
Treatment
C3A
KAI1 RNA expression normalized to HMBS
Mock
x3.5
x0.8
x2.7
x0.8
x0.7
Figure 8-II
Cell Invasion
OD (560 nm)
100%
70%
58%
74%
50%
50%
50%
Figure 8-III
Cell Migration
OD (560 nm)
100%
54%
53%
36%
33%
51%
100%
56%
73%
73%
58%
68%
100%
91%
95%
83%
68%

Figure 9A

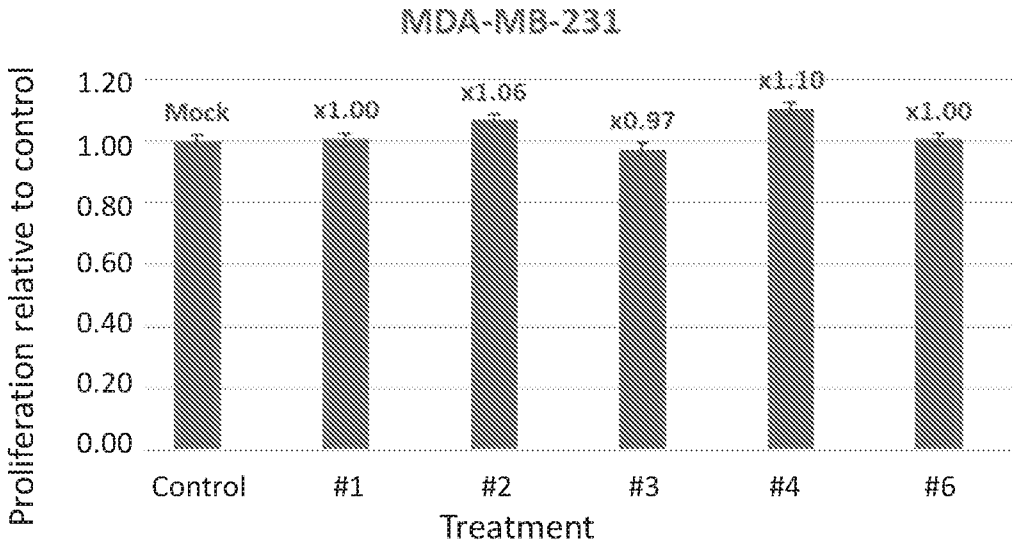


Figure 9B

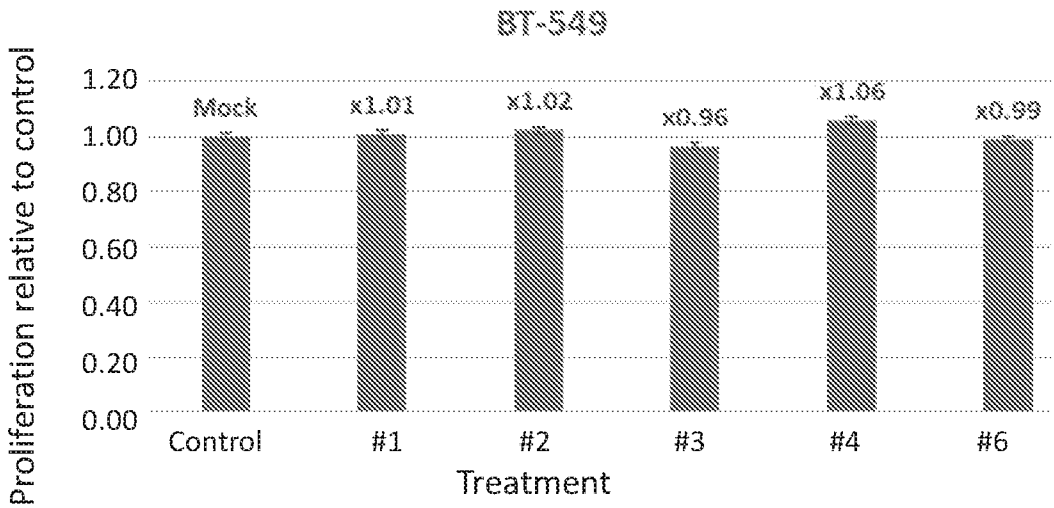


Figure 10A

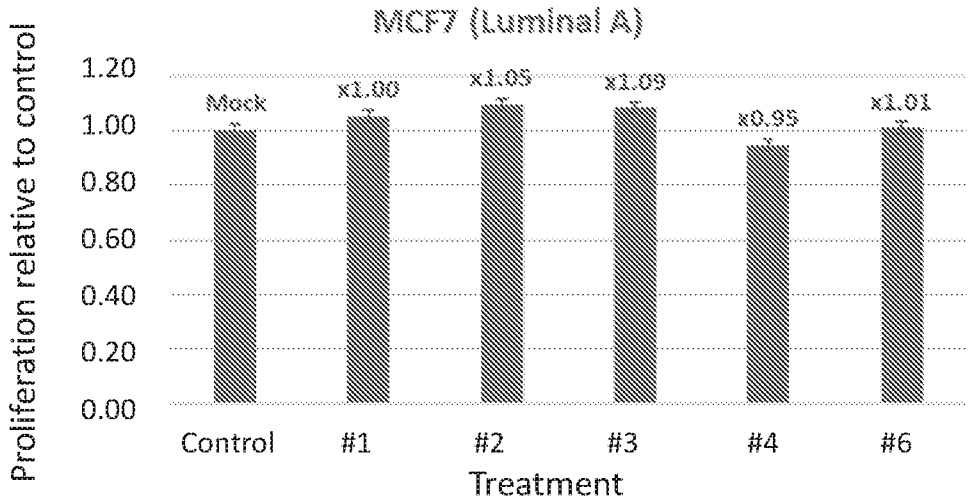


Figure 10B

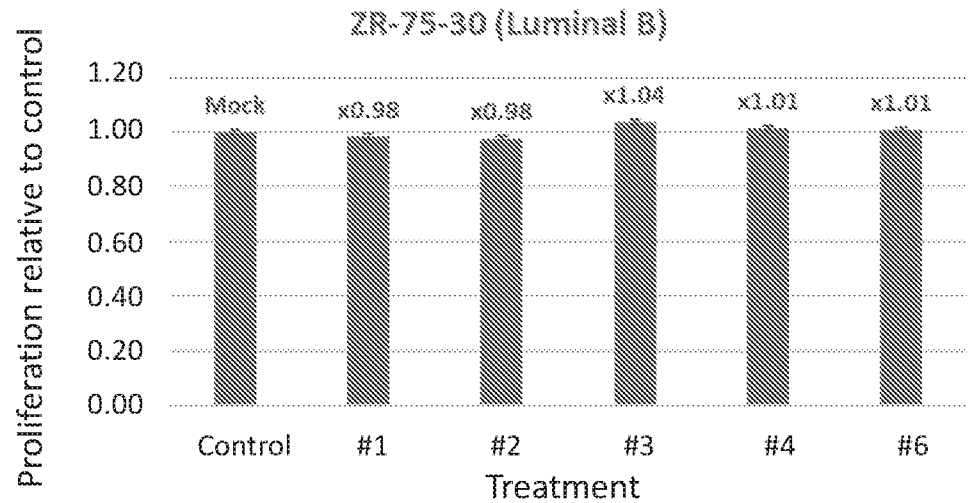


Figure 10C

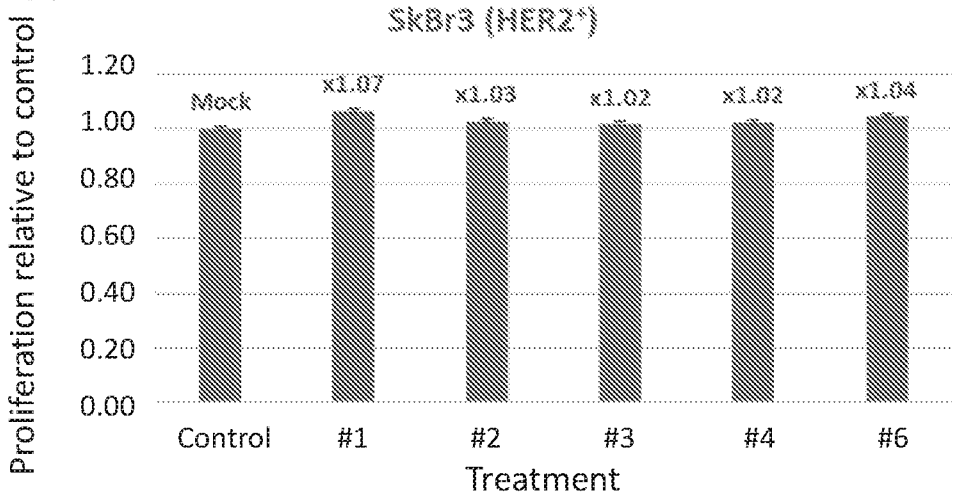


Figure 11A

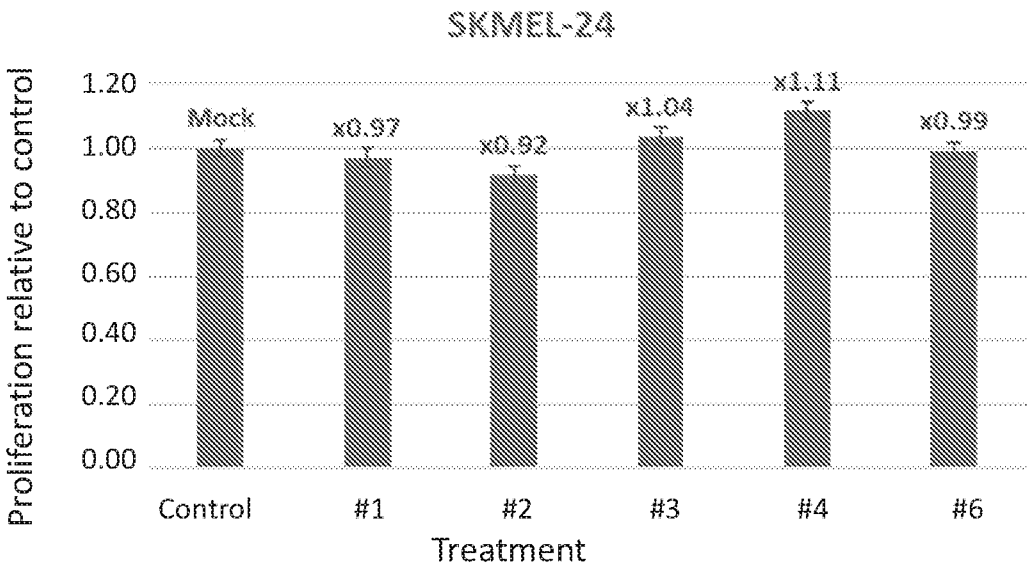


Figure 11B

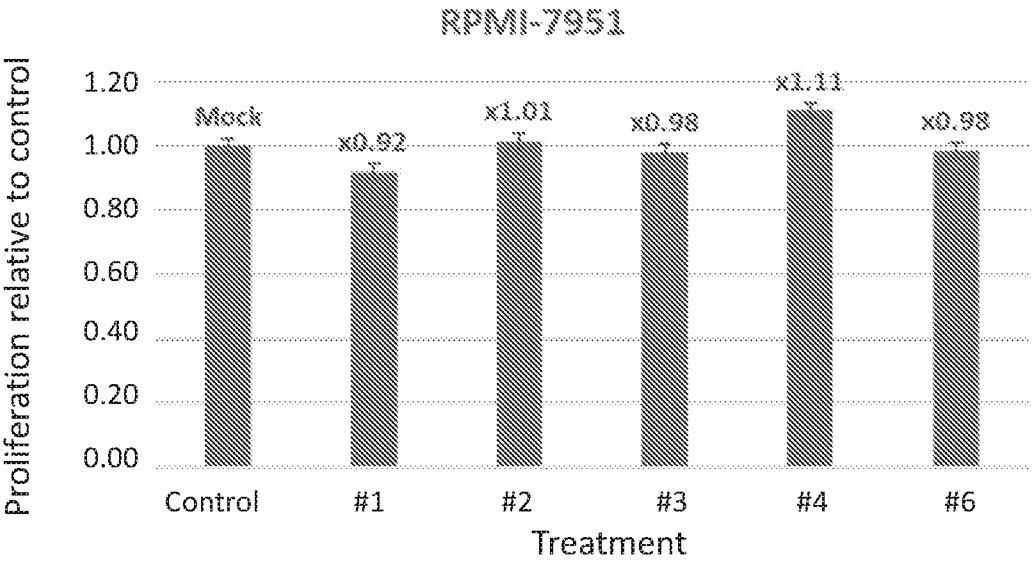


Figure 12A

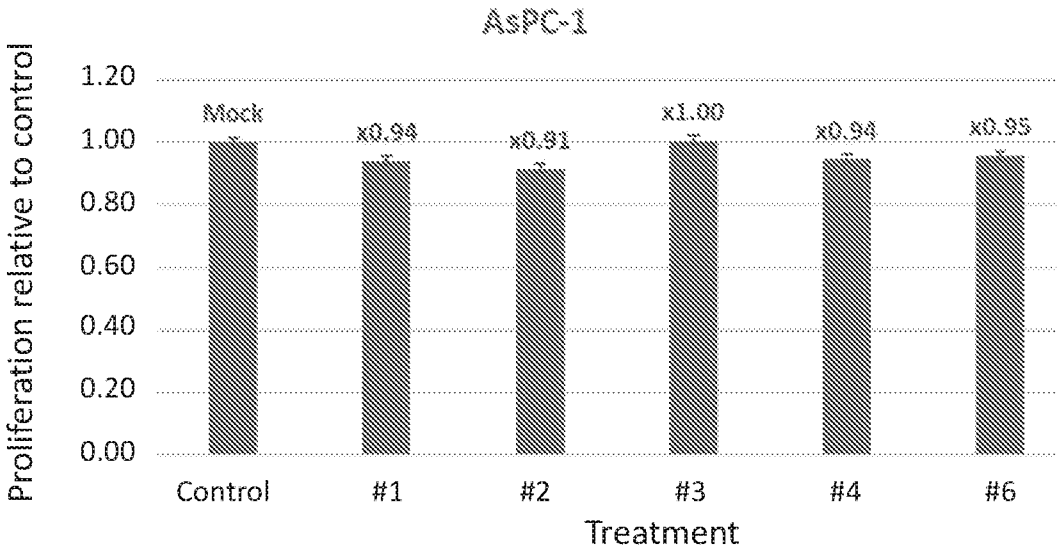


Figure 12B

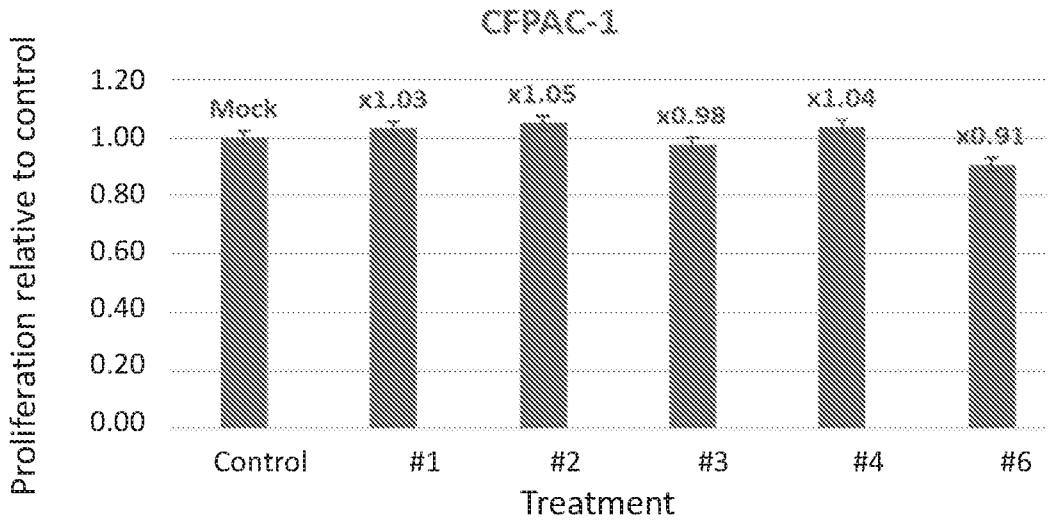


Figure 13A

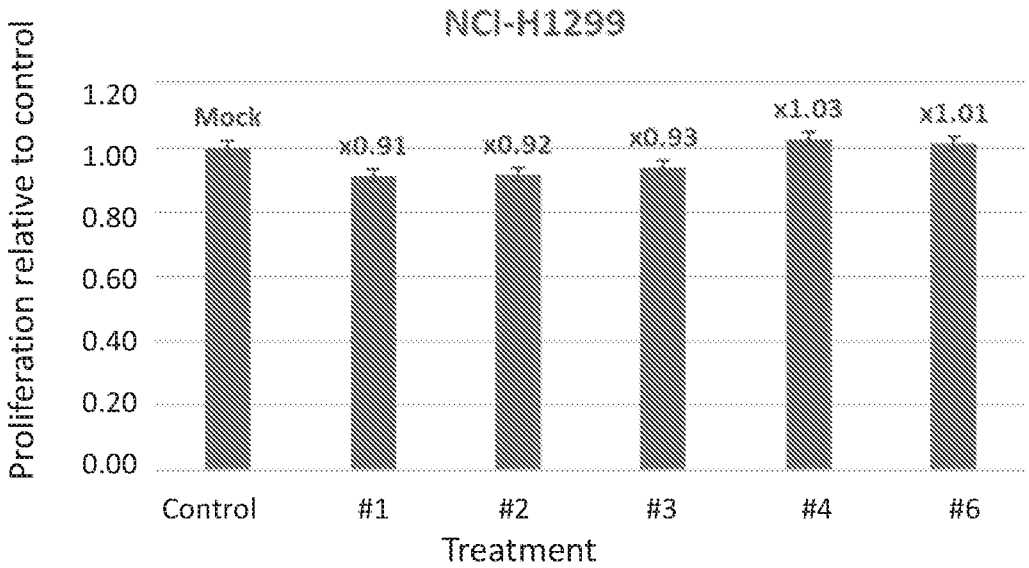


Figure 13B

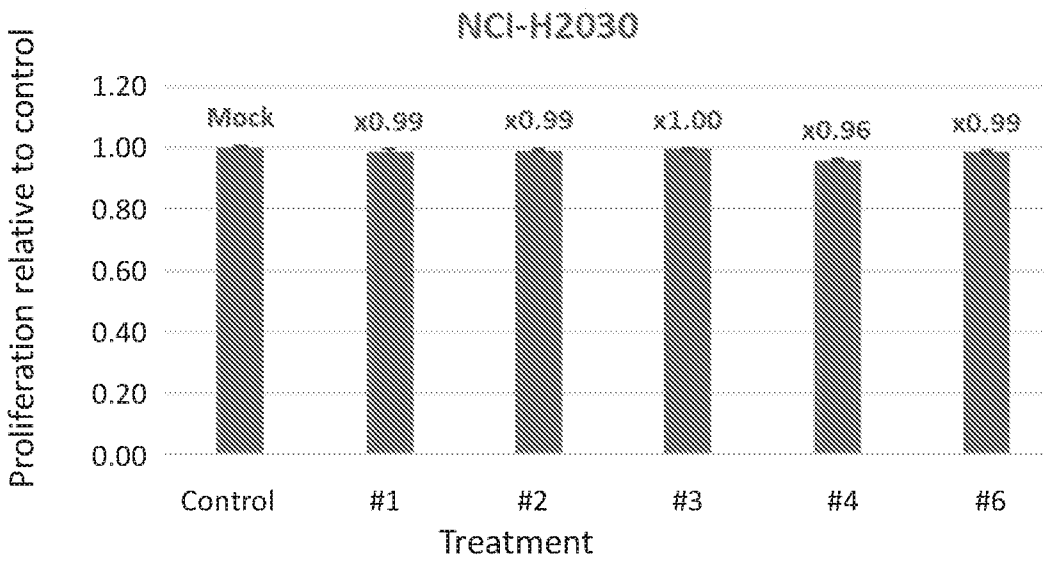


Figure 14A

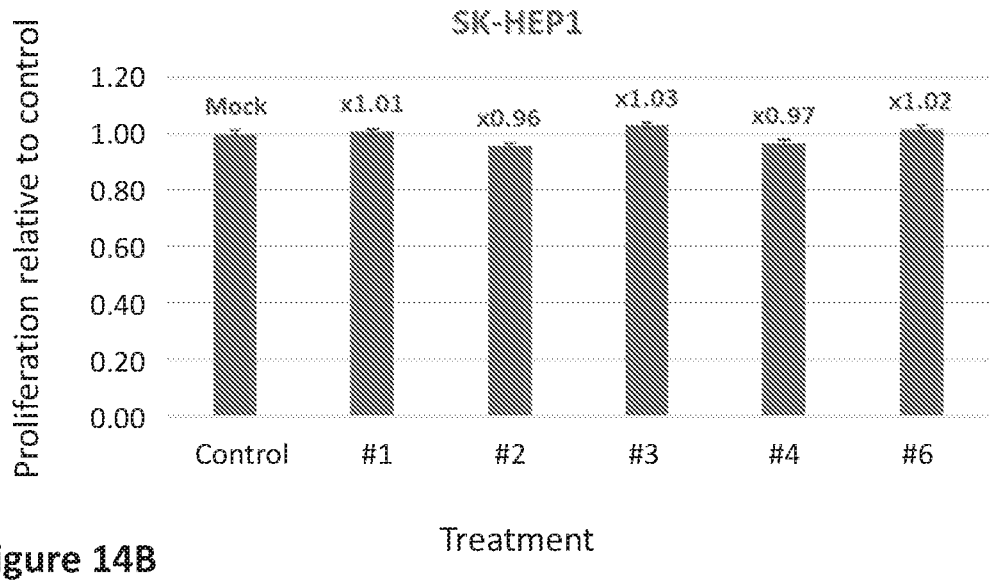
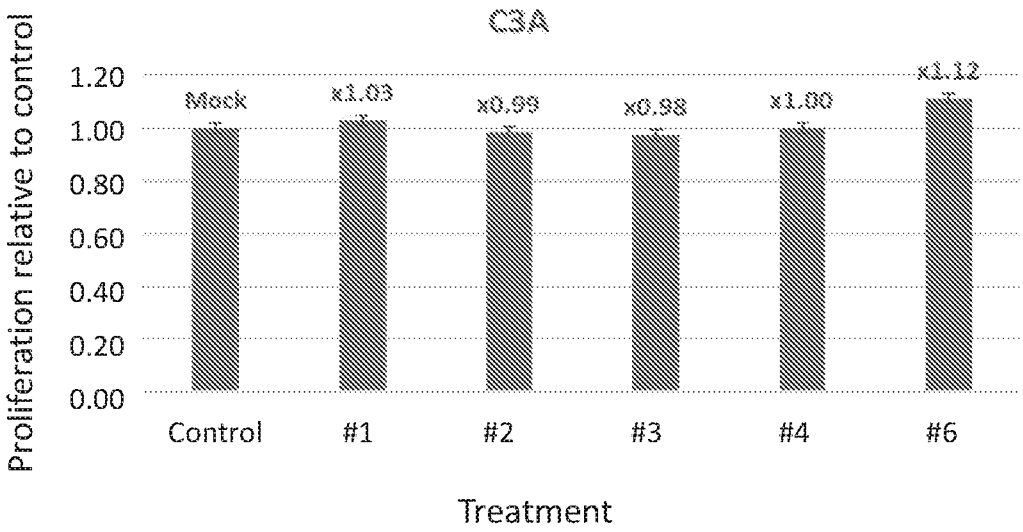


Figure 14B



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2022/050566

A. CLASSIFICATION OF SUBJECT MATTER

C07D 233/26(2022.01)i; ***C07D 233/20***(2022.01)i; ***C07D 403/14***(2022.01)i; ***A61K 31/4164***(2022.01)i; ***A61K 31/4178***(2022.01)i; ***A61K 31/53***(2022.01)i; ***A61P 35/04***(2022.01)i; ***A61P 35/00***(2022.01)i
CPC:C07D 233/26; C07D 233/20; C07D 403/14; A61K 31/4164; A61K 31/4178; A61K 31/53; A61P 35/04; A61P 35/00

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)

C07D 233/26; C07D 233/20; C07D 403/14; A61K 31/4164; A61K 31/4178; A61K 31/53; A61P 35/04; A61P 35/00
CPC:C07D 233/26; C07D 233/20; C07D 403/14; A61K 31/4164; A61K 31/4178; A61K 31/53; A61P 35/04; A61P 35/00

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

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

Databases consulted: Google Patents, CAPLUS, REGISTRY, Google Scholar, PatBase Search terms used: metasta*, cancer, breast cancer, tumor, malignant disease, proliferative disease.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1007334 A (WANDER AG DR A) 13 November 1965 (1965-11-13) page 5 lines 28-35 and page 6 lines 4-6,examples 109,121	1-6,8,10-12,14-19,21-31,33-44,49
X	Liu, Yi-Liang, et al. "Farnesyl diphosphate synthase inhibitors with unique ligand-binding geometries." ACS medicinal chemistry letters 6.3 (2015): 349-354.# Published online: 02 February 2015. DOI: <10.1021/ml500528x>.# Retrieved from URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4360152/>. Liu, Yi-Liang, et a (2015/07/02) compound 7	1-6,8-19,22-28,31,33-39,43,44,49
A	Protzel, C., et al. "Down-regulation of the metastasis suppressor protein KAI1/CD82 correlates with occurrence of metastasis, prognosis and presence of HPV DNA in human penile squamous cell carcinoma." Virchows Archiv 452.4 (2008): 369-375. Published: 28 February 2008. DOI: <10.1007/s00428-008-0590-0>. Protzel, C., et al. (2008/02/28) the whole document	1-57

☑ 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	Date of mailing of the international search report
19 July 2022	**27 July 2022**

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Telephone No. **972-73-3927136**
Email: **pctoffice@justice.gov.il**

Authorized officer
VOLKOV Karina
Telephone No.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007123553 A1 (LORUS THERAPEUTICS INC[CA]) 31 May 2007 (2007-05-31) formula I, [0001], [0142]	1,2,4-15,17-24,26-35,37-44,49,56,57
X	WO 03087026 A1 (HOFFMANN LA ROCHE[CH]) 23 October 2003 (2003-10-23) formula I, p.1 lines 1-6	1,2,4-15,17-24,26-35,37-44,49,56,57
X	WO 0126467 A1 (ONTOGEN CORP[US]) 19 April 2001 (2001-04-19) formula I, page 2 lines 1-19	1,2,4-15,17-24,26-35,37-44,49,56,57
X	WO 0224680 A1 (SMITHKLINE BEECHAM PLC) 28 March 2002 (2002-03-28) claims 1 and 11	1,2,4-15,17-24,26-35,37-44,49,56,57
X	EP 0812829 A1 (ONTOGEN CORP[US]) 17 December 1997 (1997-12-17) formula I, page 2 lines 45-60	1,2,4-15,17-24,26-35,37-44,49,56,57
X	WO 9902155 A1 (ONTOGEN CORP[US]) 21 January 1999 (1999-01-21) structure 1, page 2 lines 24-31	1,2,4-15,17-24,26-35,37-44,49,56,57
X	WO 9736587 A1 (MERCK & CO INC[US]) 09 October 1997 (1997-10-09) claim 5, page 1 lines 5-7	1,2,4-15,17-24,26-35,37-44,49,56,57
X	US 3279918 A (GEVAERT PHOTO PROD [NV]) 18 October 1966 (1966-10-18) table 1	56,57

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2022/050566

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
GB 1007334 A	13 November 1965	GB 1007334 A	13 October 1965
		AT 244958 B	10 February 1966
		AT 256866 B	11 September 1967
		DE 1445186 A1	24 October 1968
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		NO 119949 B	03 August 1970
		OA 01084 A	07 August 1968
		SE 317679 B	24 November 1969
		SE 329151 B	05 October 1970
		SE 335975 B	21 June 1971
		US 3338917 A	29 August 1967
		US 3622596 A	23 November 1971
US 2007123553 A1	31 May 2007	US 2007123553 A1	31 May 2007
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		AU 2004289539 C1	07 June 2012
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		CA 2545942 C	10 July 2012
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		EP 1692113 B1	27 September 2017
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		US 10080739 B2	25 September 2018
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		AU 2003240452 B2	04 December 2008
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		CN 1646460 A	27 July 2005
		CN 1289455 C	13 December 2006

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2022/050566

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