

Patent Annotations:

PLATINUM COMPLEX AS AN ANTICANCER AGENTS

1. **Cisplatin resistance proteins**, *Yokoyama, S., US6046044 (2000)*.

Commentary:

Cisplatin resistance genes derived from an ovarian cancer cell line and the role of nucleic acid and proteins conferring resistance to cisplatin or to heavy metals, for example cadmium and copper on sensitive cells, are reported in this invention. Different methodologies for the characterization of substances which prevent cisplatin resistance in a cell or which are chemo-sensitizers of cisplatin are discussed along with the method for identification of cisplatin resistant tumor cells using the nucleic acids and proteins discussed in this patent.

2. **Platinum complex conjugated to cyclotriphosphazene, its preparation, and anticancer agent comprising the same**, *Sohn, Y.S., Baek, H.G., Lee, C.O., US6221906 (2001)*.

Commentary:

A synthetic method for the preparation of the new oligomeric platinum complex conjugated to cyclotriphosphazene is discussed. The complex has been recognized as a potential anticancer agent due to its lower toxicity and significant anticancer activity as compared to routine anticancer drugs.

3. **Transplatinum complexes as cytotoxic and anticancer agents**, *Farrell, N., US6350740 (2002)*.

Commentary:

The invention pertains to the usage of transplatinum complexes as cytotoxic and anticancer agents. The methods for increasing water solubility of cytotoxic *trans* platinum complexes and their intended uses for the treatment of tumors by the administration of a cytotoxic platinum coordination complex of the general formula $SP4-2-[PtX(L)(L')(B)]^+$ are also discussed.

4. **Graft co-polymer adducts of platinum (II) compounds**, *Bogdanov, A., Weissleder, R., Brady, Thomas J., US5871710 (1999)*.

Commentary:

A polymeric platinum complex comprising polymeric carrier, protective chain and a reporter group may be used for the treatment of cancer as a single active agent or in combination with other chemotherapeutic agents such as cDDP, carboplatin, doxorubicin, or cyclophosphamide.

5. **Water soluble transplatinum complexes with anti-cancer activity and method of using same**, *Farrell, N.P., Bierbach, U., US6001872 (1999)*.

Commentary:

The present invention provides formulations and usage of water soluble *trans*-platinum complexes for the cure of tumors and cancer.

POLY(ADP-RIBOSE) POLYMERASE-1 (PARP-1) INHIBITORS

1. **Adenosine diphosphoribose polymerase binding nitroso aromatic compounds useful as anti-tumor and retroviral agents**, *Kun, E., Mendeleyev, J., Rice, W.G., WO9307868A1 (1993)*.

Commentary:

The invention discusses compositions of antiviral and antitumor compounds comprising 6-nitroso-1, 2-benzopyrone, 3-nitrosobenzamide, 5-nitroso-1(2H)-isoquinolinone, 7-nitroso-1(2H)-isoquinolinone, 8-nitroso-1(2H)-isoquinolinone for the prevention of viral infections and cancer.

2. **Oxo-substituted compounds, process of making, and methods for inhibiting PARP activity**, *Li, J.H., Tays, K.L., Zhang, J., WO9911624A1 and WO9911624B1 (1999)*.

Commentary:

The invention relates to the preparation, formulations and use of neuroprotective agents i.e. oxo-substituted aza-bicyclic poly-(adenosine 5-diphospho-ribose) polymerase inhibitors having nitrogen ring.

3. **Poly (ADP-ribose) polymerase PARP inhibitors, methods and pharmaceutical compositions for treating neural or cardiovascular tissue damage**, *Li, J.-H., Zhang, J., Jackson, P.F., Maclin, K.M., WO9911645A1(1999)*.

Commentary:

The invention encompasses pharmaceutical formulations of poly (ADP-ribose) polymerase inhibitors involved in the treatment of tissue damage, neurological disorders, neurodegenerative diseases, cardiovascular disorders or cancer.

4. **PARP inhibitors, pharmaceutical composition comprising same, and methods of using same**, *Jackson, P.F., Li, J.-H., Maclin, K.M., Zhang, J., WO9911649A2 (1999)*.

Commentary:

The usage of nucleic enzyme i.e. poly(adenosine 5'-diphospho-ribose) polymerase inhibitor is discussed for the prevention of cardiovascular disorders, AIDS, arthritis, atherosclerosis, cachexia, age-related macular degeneration, and cancer, and also for stimulating damaged neurons resulting from ischemia and reperfusion injury. The degenerative diseases of skeletal muscle, diabetes, head trauma, immune senescence, inflammatory bowel disorders i.e. colitis and Crohn's disease, muscular dystrophy,

osteoarthritis, osteoporosis, chronic and acute pain e.g. neuropathic pain, renal failure, retinal ischemia, septic shock (endotoxic shock), and skin aging are also prevented by inhibitors of the nucleic enzyme poly (adenosine 5'-diphospho-ribose) polymerase ["poly(ADP-ribose) polymerase II or IIPARP11 which is also sometimes called "PARS" for poly(ADP-ribose) synthetase].

- 5. Benzimidazole compounds**, *Griffin, R.J., Calvert, A.H., Curtin, N.J., Newell, D.R., Golding, B.T., WO9704771A1 (1997)*.

Commentary:

The invention describes the use of benzimidazole-4-carboxamide derivatives for inhibiting activity of DNA repair enzyme, poly(ADP-ribose) polymerase or PARP enzyme. These compounds are used with cytotoxic drugs or in radiotherapy for antitumor remedies.

- 6. Substituted 2-phenylbenzimidazoles, the production thereof and their use**, *Lubisch, W., Kock, M., Hoger, T., WO0026192A1 (2000)*.

Commentary:

This invention describes the process of preparation of enantiomeric and diastereomeric forms of 2-phenyl-benzimidazoles and the treatment of neurodegenerative diseases, epilepsy, ischemic damage, myocardial infarction, and tumors by phenyl-benzimidazole carboxamide derivatives acting as beneficial polymerase inhibitors.

MATRIX METALLOPROTEINASE INHIBITORS

- 1. Low molecular weight components of shark cartilage, processes for their preparation and therapeutic uses thereof**, *Dupont, E., Lachance, Y., Lessard, Y., Auger, S., US20010001041A1 (2001)*.

Commentary:

The invention provides details of uses and production of low molecular weight 500kDa constituents of shark cartilage. The aqueous and organic extracts of these components showed anti-MMP activity against matrix metalloprotease and also possess antitumor and anti-angiogenic activities.

- 2. Matrix metalloprotease production inhibitor**, *Yano, A., Ogawa, K., Yoshida, T., Nekado, H., Nonomura, M., Isawa, A., Sato, T., Mimaki, Y., Sashita, Y., Ito, A., JP2000080035A2 (2000)*.

Commentary:

The invention relates to the inhibition of enzymes of collagenase, gelatinase and stromelysin groups by different substitutions in a polyalkoxyflavonoid moiety. This polyalkoxyflavonoid is responsible for the inhibition of matrix metalloprotease production and its precursors. This inhibitor is used for the treatment of cancer, chronic rheumatism, arthrosis deformans, etc.

- 3. MMP inhibitor**, *Akisawa, T., Yahara, M., Hashimoto, F., Yamada, M., Suma, Y., Kono, T., Uchida, K., Oshiba, Y., JP2000226329A2 (2000)*.

Commentary:

The invention claims the role of active constituent catechin in matrix metalloprotease inhibitor for the cure of refractory diseases such as rheumatoid arthritis, HIV infectious disease or diabetes complication.

CLINICAL EFFICACY IN HEMATOLOGICAL MALIGNANCIES

- 1. Cyclodextrin cladribine formulations**, *Schultz, T.W., Naeff, R., US6194395 (2001)*.
- 2. Oral formulations of cladribine**, *Bodor, N.S., Dandiker, Y., WO04087101A2 and WO04087101A3 (2004)*.

Commentary:

The invention pertains to the oral, liquid and injectable dosage forms of aqueous solution of a mixture of cladribine for (2-chloro-2'-deoxyadenosine; 2-CdA) and cyclodextrin for intramuscular and subcutaneous administration.

- 3. Oral administration of adenosine analogs**, *Wrenn, S.M. Jr., US6174873 (2001)*.

Commentary:

Hematological malignancies, stroke, myocardial infarction or inflammation are treated with compositions comprising adenosine derivatives. These compositions are in different dosage forms i.e. as pills, capsules, lozenges or tablets.

INTRACELLULAR CALCIUM AND ANGIOGENESIS

- 1. Methods of modulating and of identifying agents that modulate intracellular calcium**, *Roos, J., Stauderman, K.A., Velicelebi, G., Ohlsen, K.L., Digregorio, P., WO04078995A2 (2004)*.

Commentary:

The invention provides methods for the characterization of agents and proteins responsible for modulating intracellular calcium within cells. The agents are claimed for treating autoimmune disease, asthma, arthritis, etc.

- 2. Intracellular calcium concentration increase inhibitors**, *Mikoshiba, K., Iwasaki, H., Maruyama, T., Hamano, S.-I., US20040259842A1 (2004)*.

Commentary:

The invention is concerned with the treatment of platelet aggregation, ischemic diseases in heart and brain, immune deficiency diseases, allergosis, bronchial asthma, hypertension, cerebrovascular spasm, various renal diseases, pancreatitis, Alzheimer's disease by the borate compounds as an active ingredient in the composition. A boron compound in this composition inhibits intracellular calcium concentration.

- 3. Calcium channel drugs and uses**, *Ji, Y.-H., Natarajan, M., Griffin, J.H., Jenkins, T.E., US6897305 (2005)*.

Commentary:

The multibinding compounds constitute 2-10 ligands covalently bonded and modulating activity of Ca²⁺ channel

for preventing disorders in mammals due to an activity of a Ca^{2+} channel.

4. **Screening assays intramitochondrial calcium**, *Murphy, A.N., Stout, A.K., US20050170329A1 (2005).*

Commentary:

The invention describes screening methods for agents claimed to facilitate mitochondrial regulation of intracellular calcium. These agents are used as a remedy for the cure of disorders resulting from abnormal mitochondrial function.

INHIBITORS FOR METASTASIS DEVELOPMENT

1. **Cancer metastasis inhibitor**, *Ochiai, A., Shitara, K., Nakamura, K., Oki, Y., WO05018671A1 (2005).*

Commentary:

The invention discloses insulin-like growth factors IGF-I and IGF-II for the treatment of bone metastasis and liver metastasis and significant inhibition of cancer metastasis.

2. **CXCR4 chemokine receptor binding compounds**, *Bridger, G., McEachern, E.J., Sherlj, R., Schols, D., US20040209921A1 (2004).*

Commentary:

Formulations of pyridine compounds with different substituents that bind to chemokine receptors and which can be used for treatment of aplastic anemia, leukemia, drug-induced anemia, HIV, inflammation, asthma, cancer and rheumatoid arthritis, and for regenerating cardiac tissue, enhance stem cells and white blood cells count are discussed.

3. **Use of chemokine receptor antagonist for the treatment and inhibition of metastasis, functions as ligand for the CXCR4 receptor**, *Burger, J.A., DE10240064A1 (2004).*

Commentary:

The invention pertains to the usage of chemokine receptor antagonist for the treatment of cancer and inhibition of metastasis. The activity is attributed to ligand for the CXCR4 receptor.

4. **Application of acetyl boswellic acid in preparing antitumor agent**, *Rui, H., Wanzhou, Z., Zhaodi, F., CN1436533A (2003).*

Commentary:

The invention describes antitumor activity of acetyl boswellic acid (BC-4) isolated from *Boswellia carterii*. Acetyl boswellic acid acts as a tumor metastasis inhibitor and prevents proliferation of human umbilical vein endothelial cell, inhibits animal's grafted tumor and metastasis of malignant tumor, and also shows minimum toxicity.

5. **Integrin expression inhibitors**, *Haneda, T., MX2007249A (2002).*

Commentary:

The invention provides usage of integrin expression inhibitors comprising the active ingredient containing a

sulfonamide moiety for preventing arteriosclerosis, psoriasis, cancer, osteoporosis, retinal angiogenesis, diabetic retinitis, or inflammatory diseases and anticoagulant agents.

6. **Peptides with 1 integrin subunit dependent cell adhesion modulating activity**, *McCarthy, J.B., Furcht, L.T., Frey, A.B., US6849712 (2005).*

Commentary:

The invention relates to the property of alpha4beta1 integrin dependent adhesion in tumor cell biology and discusses modulation of beta1 integrin subunit comprising amino acids in the sequence Pro-Arg-Ala-Arg-Ile-Tyr (SEQ ID NO:24), Arg-Ala-Arg-Ile-Tyr (SEQ ID NO:25), Ala-Arg-Ile-Tyr (SEQ ID NO:26), or Arg-Ile-Tyr with C-terminal Ile-Tyr dipeptide sequence.

CYTOTOXICITY OF CIS-PLATINUM COMPLEX

1. **Method of reducing toxicity of anticancer agent**, *Rustum, Y.M., Cao, S., Durrani, F., US20040180099 (2004) and US20040110838A1 (2004).*

Commentary:

The invention discusses the process of reducing toxicity of oxaliplatin and doxorubicin. These selenium compounds may be administered prior, during or after the administration of the anti-cancer agents.

3. **Combination chemotherapy**, *Smith, M.P., Stephens, T.C., US20040053882A1 (2004).*

Commentary:

The present invention discusses a combination product comprising a sterically hindered platinum coordination compound (SP-4-3)-(cis-aminedichloro-[2-methylpyridine] platinum (II) or a prodrug and a non-platinum based anticancer agent i.e. Taxol, Gemcitabine, Navelbine, Doxil, etc. with a carrier or diluent. The combination product is used for the treatment of human cancer.

4. **Pharmaceutical agents**, *Marson, C., WO05011661A1 (2005).*

Commentary:

The invention describes the prevention of cancer, cardiac hypertrophy, histone deacetylase mediated and hematological disorders and genetic-related metabolic diseases by different formulations of aromatic compounds. Aromatic compounds are also used in combination with other anticancer agents for the treatment of cancer.

5. **Method for treating cancer in humans**, *Hwu, P., Wang, G., US20050063947A1 (2005).*

Commentary:

The invention is related to the treatment of cancer in humans with IL-21 polypeptide, polynucleotide and vector, comprising an IL-21 nucleic acid sequence encoding an IL-21 polypeptide, variants and fragments.

6. **Antitumor agents**, *McMorris, T.C., Kelner, M.J., US6855696 (2005).*

Commentary:

The method of preparation of illudin analogs, intermediates and their usage for the prevention of the cancer is described in this invention.

- Cytotoxic compounds**, *Uckun, F.M., Jan, S.-T.M. US20040229935A1 (2004)*.

Commentary:

The invention pertains to the inhibition of cell proliferation or cytotoxicity in leukaemia cells by compounds possessing furan, thiophene, thiazole, oxazole, or imidazole group at one end of the molecule (head) and a hydrophobic, aliphatic chain at the other end of the molecule (tail). The inhibitory action is attributed to the binding of the compounds with tubulin, causing tubulin depolymerization.

- Combination methods of treating cancer**, *Bacopoulos, N.G., Chiao, J.H., Marks, P.A., Miller, T.A., Paradise, C.M., Richon, V.M., Rifkind, R.A., WO05023179A2 and WO05023179A3 (2005)*.

Commentary:

The invention describes the process of treating cancer with suberoylanilide hydroxamic acid in combination with vincristine, vinblastine (known potential anti-cancer agents). Histone deacetylase (HDAC) inhibitor is administered followed by suberoylanilide hydroxamic acid and the anti-cancer agent.

INHIBITOR OF APOPTOSIS PROTEINS (IAPS)

- Antisense IAP oligonucleotides and uses thereof**, *Korneluk R.G., MacKenzie, A.E., Liston, P., Baird, S., Tsang, B.K., Pratt, C., US2004127694A1 (2004)*.

Commentary:

The method for using antisense IAP oligonucleotides, negative regulators of the IAP and antisense inhibitors of apoptosis nucleic acid for the prevention of cancer is discussed. The antisense inhibitor of apoptosis nucleic acid potentiates apoptosis in a cell.

- IAP nucleobase oligomers and oligomeric complexes and uses thereof**, *LaCasse E., McManus, D., WO05042558A1 (2005)*.

Commentary:

The present invention features methods for inhibition of expression of an IAP polypeptide and for the induction of apoptosis in a cell with nucleobase oligomers and oligomer complexes i.e. XIAP, hIAP-1 or hIAP-2. The combination therapy of these complexes with chemotherapeutic agents is also discussed.

- RNA interference mediated inhibition of XIAP gene expression using short interfering nucleic acid (siNA)**, *McSwiggen, J., Chowrira, B.M., WO05014811A2 (2005)*.

Commentary:

This invention also relates to compounds, compositions and methods for nucleic acid molecules, i.e. short interfering nucleic acid (siNA), RNA (siRNA), double-stranded RNA

(dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) involved in modulating XIAP gene expression.

- Methods and composition for derepression of IAP-inhibited caspase**, *Reed, J.C., Houghton, R.A., Nefzi, A., Ostresh, J.M., Pinilla, C., Welsh, K., WO03045974A2 and WO03045974A3 (2003)*.

Commentary:

The invention features usage of isolated agents comprising core peptide (from core peptides 5 to 39 and 42 to 55). The isolated agents are used for the treatment of cancer via inhibiting IAP-inhibited caspase.

- Activators of caspases**, *Wang, X., Du, C., WO0149719A2 and WO0149719A3 (2000)*.

Commentary:

The diagnostic characterization of binding agents and their applications is claimed to be achieved by caspase regulatory polypeptides and polynucleotide sequences compositions.

- Apoptotic compounds**, *Wang, X., Du, C., WO0216402A2 and WO0216402A3 (2000)*.

Commentary:

The invention relates to the enhancement of apoptosis of tumor cells in cancers associated with breast, prostate, lung and ovarian cancer or sarcoma by peptide i.e. AV peptoid. Assays for identifying agents involved in modulation of AV with an IAP and composition for enhancing the apoptosis of pathogenic cells, particularly tumor cells, e.g. breast cancer, prostate cancer, lung cancer, colon cancer, ovarian cancer or sarcoma, comprise apoptotic compounds.

- Peptides derived from smac (DIABLO) and methods of use thereof**, *Fesik, S.W., Meadows, R.P., Betz, S.P., Liu, Z., Olejniczak, E.T., Sun, C., WO0230959A2 and WO0230959A3 (2002)*.

Commentary:

The isolation of peptide wild-type human smac (DIABLO) protein and the usage for the characterization of apoptosis inducing agents in cells is described.

- Compositions and methods for regulating apoptosis**, *Shi, Y., WO0226775A2 and WO0226775A3 (2002)*.

Commentary:

The methods for using peptides and peptidomimetics in the promotion of apoptosis in cells by the interaction with Smac/DIABLO, Hid, Grim and Reape (IAP-binding proteins) are disclosed. Synthetic tetrapeptide, its mimetic is used for rational drug design.

- An IAP binding peptide or polypeptide and methods of using the same**, *Alnemri, E.S., WO0216418A2 and WO0216418A3 (2002)*.

Commentary:

The invention provides usage of Smac peptides and polynucleotides, encoding peptides for modulating apoptosis

in neoplastic cell and binding to a portion of inhibitor of Apoptosis protein.

10. **Smac-peptides as therapeutic against cancer and autoimmune diseases**, *Debatin, K.M., Fulda, S., EP1354952A1 (2003)*.

Commentary:

The invention describes the use of smac antagonists for apoptosis regulation and treatment of cancer and autoimmune diseases.

11. **Omi and domains thereof that disrupt IAP-Caspase interaction**, *Alnemri, E.S., WO03006680A2 and WO03006680A3 (2003)*.

12. **Compositions and methods for cleaving IAP**, *Stowers Institute for Medical Research, WO2004072241A2 (2004)*.

Commentary:

The invention features function of Omi nucleic acids and peptides for the modification and regulation of caspase-mediated apoptosis. The isolated nucleic acid molecule comprising a polynucleotide is used as a remedy for the treatment of cancer, tumor, or autoimmune disorders.

13. **XAF genes and polypeptides: methods and reagents for modulating apoptosis**, *Korneluk, R.G., Tamai, K., Liston, P., Mackenzie, E., US2003215824A1 (2003)*.

Commentary:

The invention discloses human XAF polypeptides, anti-XAF antibodies and XAF nucleic acid sequences, which react with the inhibitors of apoptosis proteins and are used as diagnostic reagents for the treatment of cancer, neurodegenerative disorders and apoptotic conditions, including HIV.

14. **Livin-derived peptides, compositions and uses thereof**, *Ben-Yehuda, D., Ashhab, Y., Nachmias, B., WO04106371A1 (2004)*.

Commentary:

The invention describes process and composition for potentiating the sensitivity of cells to death-inducing treatments or agents constituting p30-Livin alpha and p28-Livin beta derived from pro-apoptotic peptides.

15. **Method to identify modulators of survivin-tubulin interactions**, *Altieri, D.C., WO9950440A2 and WO9950440A3 (1999)*.

16. **Methods for selectively modulating surviving apoptosis pathways**, *Altieri, D.C., US20030143232A1 (2003)*.

17. **Detection of survivin in the biological fluids of cancer patients**, *Altieri, D.C., Weiss, R.M., WO04112570A3 (2004)*.

Commentary:

The present invention relates to methods and compositions for identifying agents that promote survivin regulated apoptosis by modulating the interactions between survivin and polymerized tubulin or the mitotic spindles.

18. **Survivin promotion of angiogenesis**, *Altieri, D.C., MX2006167A (2004)*.

Commentary:

The invention features usage of agents involved in the prevention and treatment of ischemic disease caused by myocardial infarction, stroke and angiogenesis via a process of inhibiting survivin or survivin activity.

CHECKPOINT 1 INHIBITORS

1. **Aminopyrazole compounds and use as CHK1 inhibitors**, *Johnson, M.D., Teng, M., Zhu, J., WO05009435A1 (2005)*.

Commentary:

The invention describes certain aminopyrazole compounds for the treatment of cancer, Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma, leukemia and lymphomas by stimulating the activity of checkpoint kinase. New aminopyrazole compounds are checkpoint kinase 1 inhibitors useful to treat cancer, Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma, leukemia and lymphomas. The compounds are used alone or in combination with anti-cancer agents.

2. **Pyrazoloquinoline derivatives as CHK-1 inhibitors**, *Boyle, R.G., Imogai, H.J., Cherry, M., Humphries, A.J., Navarro, E.F., Owen, D.R., Dales, N.A., Lamarche, M., Cullis, C., Gould, A.E., WO05028474A2 and WO05028474A3 (2005)*.

Commentary:

The usage of 2,5-dihydro-pyrazolo(4,3-c)quinolin-4-one compounds as CHK1 inhibitors for the treatment of cancer is discussed.

3. **CHK-1 inhibitors**, *Boyle, R.G., Imogai, H.J., Cherry, M., US20040014765A1 (2004)*.

Commentary:

The invention describes a method for treatment of cancer with diarylurea compounds acting as checkpoint kinase-1 inhibitors.

4. **Carbamate compositions and methods for modulating the activity of the CHK1 enzyme**, *Rui E.Y., Johnson, T.O., Kellum J.H., US20050148643 (2005)*.

Commentary:

The invention presents the composition of benzimidazol-2-yl-methyl phenylcarbamate compounds for the prevention of benign hyperplasia of the skin, benign hyperplasia of prostate and cancer in combination with anti-neoplastic agents.

5. **Indazole compounds and pharmaceutical compositions for inhibiting protein kinases, methods for their use**, *Kania, R.S., Bender, S.L., Borchardt, A.J., Cripps, S.J., Palmer, C.L., Tempczyk-Russell, A.M., US20050124662A1 (2005)*.

Commentary:

The invention deals with the method and compositions of 3, 6-disubstituted indazole derivatives that promote or inhibit the activity of protein kinases in diseases i.e. retinopathies, psoriasis, rheumatoid arthritis, cancer, neovascular glaucoma, age-related macular degeneration and angiogenesis.

6. **Compounds useful for inhibiting CHK1**, Keegan, K.S., Kesicki, E.A., Gaudino, J.J., Cook, A.W., Cowen, S.C., Burgess, L.E., US20030069284A1 (2003).

Commentary:

Aryl- and heteroaryl-substituted urea compounds are used as remedies for cancer, DNA damage or lesions in DNA replication, chromosome segregation, cell division and inflammatory conditions. A method for the preparation of checkpoint kinase I inhibitors is also given.

7. **Fused tri and tetracyclic pyrazole kinase inhibitors**, Tong, Y., Claiborne, A.K., Li, G., Lin, N.-H., Sham, H.L., Sowin, T.J., Tao, Z.-F., US20040259904A1 (2004).

Commentary:

The present invention discloses a process of preparing and using tri- and tetra-cyclic pyrazole derivatives in the treatment of tumors of the brain, nerves, eyes and meninges as well as cancer, primary and metastatic solid tumors and carcinomas.

8. **Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy**, Benedict, S., Bennett, M., Ninkovic, S., Teng, M., Rui, Y., Wang, F., US20050075499A1 (2005).
9. **Heterocyclic kinase inhibitors**, Haswold, L.A., Hexamer, L., Li, G., Lin, N.-H., Sham, H., Sullivan, G. M., Wang, L., Xia, P., US20040254159A1 (2004).

10. **Diazepinoindole derivatives as kinase inhibitors**, Ninkovic, S., Bennet, M.J., Rui, Y., Wang, F., Benedict, S.P., Teng, M., WO04063198A1 (2004).

Commentary:

New diazepinoindole derivatives are claimed as protein kinase inhibitors for the treatment of cancer.

11. **Macrocyclic kinase inhibitors**, Tao, Z.-F., Lin, N.-H., Wang, L., Sowin, T.J., US20050096324A1 (2005).

Commentary:

The invention features the use of cyclic urea derivatives as inhibitors of protein kinases and cancers i.e. primary and metastatic solid tumors including carcinomas of breast, colon, rectum, lung, stomach, pancreas, liver and gallbladder.

12. **Urea kinase inhibitors**, Li, G., Li, Q., Li, T., Lin, N.-H., Mantei, R.A., Sham, H.L., Wang, G.T., US20040259885A1 (2004).

Commentary:

The invention pertains to the preparation, compositions and use of urea derivatives for the treatment of Kaposi's sarcoma, solid tumors, and for inhibiting protein kinase inhibitors

13. **Chk-, Pdk- and Akt-inhibitory pyrimidines, their use as pharmaceutical agents**, Bryant, J., Kochanny, M.J., Yuan, S., Khim, S.-K., Buckman, B.O., Arnaiz, D.O., Bomer, U., Briem, H., Esperling, P., Huwe, C., Kuhnke, J., Schafer, M., Wortmann, L., Kosemund, D., Eckle, E., Feldman, R.J., Phillips, G.B., US20040186118A1 (2004).

Commentary:

The present invention discloses preparation, formulations of pyrimidine derivatives acting as kinase inhibitors for the cure of cancer, autoimmune disorders, cardiovascular diseases, eye disorders and nephrological diseases.