In 1991, Merck, the pharmaceutical giant, struck a landmark deal with the private non-profit National Biodiversity Institute, INBio, in Costa Rica to pay for millions of dollars worth of royalties, equipment and supplies to InBio whose scientists would collect plants, insects and microorganisms from the protected jungles of Costa Rica for Merck scientists to research for use as potential pharmaceutical agents. The agreement gave Merck patent rights over any chemicals discovered. These types of agreements came to be known as “bioprospecting” as they were so similarly constructed to those regarding mineral exploration. Since between 50-80% of all pharmaceuticals are derived from natural materials, and habitat diversity is steadily trending down, these agreements have not been without controversy, but they also have not been very productive: to date, Merck has not been able to realize any profit from the agreement. So why persist? See if you can develop some understanding through these two articles.

You will need to access the following links to complete this worksheet, as well as do “Google” searches (&/or use your notes &/or drug handbook). The worksheet isn’t designed to test your understanding so much as help you review drugs we have covered. Yes, it is long, but not hard to complete.

* [*Cashing in on nature’s pharmacy*](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1083874/), Lisa Onaga, EMBO Rep 2011 April 15; 2(4):263-265. The link goes to the National Institutes of Health, National Library of Medicine, National Center for Bioinformatics to read this archived article by Lisa Onaga. This is a general interest article and VERY easy to read. Complete the three questions using this article.
* [*Natural Products as Sources of New Drugs over the Last 25 Years*,](http://www.icbg.org/documents/np030096l.pdf) David Newman and Gordon Cragg. J.Nat.Pro. 2007 70:461-477. This is a research review article and will take effort to dig through. Complete the 1st several tables using this article. Use “Google” etc., for the last table.

1. In Lisa Onaga’s article, she quotes Lynn Caporale, a former Senior Director at Merck who states that “the molecular diversity found in nature has…”\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_”
2. Scale remains perhaps the biggest obstacle. Onaga writes, “the chance of a successful hit is one in 10 000 for synthetic compounds, while the rate for natural products is as low as one in \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.
3. The pharmaceutical companies persist, even though there haven’t been any big benefits yet to these agreements, because of the statistical fact: “the total number of natural samples that have been tested so far is \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_”

The following table summarizes information from “Natural Products as Sources of New Drugs…” about drugs we cover in PHRM 203, derived from natural products. The paper is incomplete and I’ve added in the names of drugs not listed. I’ve listed the generic names as they appear in the paper to make searching faster.

|  |  |
| --- | --- |
| **Antibacterials** | |
| Generic name | Trade name |
| Azithromycin |  |
| Aztreonam |  |
| Cefepime |  |
| Dalfopristin |  |
| Erythromycin |  |
| Quinupristin |  |
| Ciprofloxacin |  |
| Linezolid |  |

|  |  |
| --- | --- |
| **Antifungals** | |
| Generic name | Trade name |
| Fluconazole |  |

|  |  |
| --- | --- |
| **Antivirals** | |
| Generic name | Trade name |
| Interferon alfa |  |
| Interferon alfa-2b |  |
| Enfuvirtide |  |
| Efavirenz |  |
| Foscarnet |  |
| Imiquimod |  |
| Nevirapine |  |
| Oseltamivir |  |
| Acyclovir |  |
| Emtricitabine |  |
| Ganciclovir |  |
| Lamivudine |  |
| Tenofovir |  |
| Atazanavir |  |
| Darunavir |  |
| Fosamprenevir |  |
| Lopinavir |  |
| Ritonavir |  |

|  |  |
| --- | --- |
| **Antiparasiticals** | |
| Generic name | Trade name |
| Ivermectin |  |
| Mefloquine |  |
| Albendazole |  |
| Chloroquine | Aralen |

|  |  |
| --- | --- |
| **Anticancer (see table 9)** | |
| Generic name | Trade name (look up) |
| Interferon alfa2a |  |
| Interferon gamma-1a |  |
| Asparaginase |  |
| Doxorubicin |  |
| Paclitaxel |  |
| Testosterone |  |
| Vincristine |  |
| Dexamethasone |  |
| Ethinyl estradiol |  |
| Etoposide |  |
| Leuprolide |  |
| Prednisone |  |
| Chlorambucil |  |
| Tamoxifen |  |
| Methotrexate |  |

|  |  |
| --- | --- |
| **Antidiabetes drugs** | |
| Generic name | Trade name |
| Insulin aspart |  |
| Insulin determir |  |
| Insuling glargine |  |
| Insulin glulisine |  |
| Insulin Lispro |  |
| Acarbose |  |
| Pioglitazone |  |

|  |  |  |
| --- | --- | --- |
| **Others from class not listed in article (you may simply “Google” these names)** | | |
| Generic name | Trade name | Source or Based on |
| Adapalene |  | Retinoid related to vitamin A |
| Adenosine |  | Natural purine |
| Allopurinol |  | A xanthine oxidase inhibitor that is an analog of hypoxanthine, the precursor of xanthine, a critical metabolite for purines that is further metabolized to uric acid. |
| Alteplase |  | Recombinant form of tissue plasminogen activator (t-PA) |
| Amoxicillin |  | Semi-synthetic related to ampicillin |
| Aprotinin |  | Natural protease inhibitor extracted from bovine lungs |
| Aspirin |  | Synthesized from salicylates isolated from willow and other plants |
| Atorvastatin |  | Synthetic Fungal metabolite-derived HMG-CoA reductase inhibitor |
| Atropine |  | ***Atropa belladonna*** (deadly nightshade) and other plants in the ***Solanaceae*** family |
| Beractant |  | Natural bovine lung extract of lung surfactant |
| Bivalirudin |  | Leech spit |
| Bromocriptine |  | Derived from the ergot (the fungus ***Claviceps purpurea***) alkaloid ergocriptine (as is LSD, by the way). |
| Buprenorphine |  | Semi-synthetic thebaine derivative (opioid) |
| Calcitonin, salmon |  | From salmon |
| Captopril |  | Snake spit (Brazilian pit viper) |
| Castor oil |  | Extract of castor beans |
| Cephalexin |  | Beta lactam antibiotic derived from the fungus ***Acremonium*** |
| Clindamycin |  | Based on lincomycin (see lincomycin) |
| Colchicine |  | Autumn crocus (meadow saffron) extract |
| Dextromethorphan |  | Semi-synthetic opioid antitussive |
| Digoxin |  | Cardiac glycoside from foxglove, ***Digitalis purpurea*** |
| Diphenoxylate |  | Semi-synthetic opioid |
| Dopamine |  | Catecholamine |
| Doxycycline |  | Based on oxytetracycline from the soil actinomycete, ***Streptomyces rimosus*** |
| Dronabinol |  | Synthetic Tetrahydrocannabinol (THC), the active component of ***Cannabis sativa (***marijuana) |
| Enoxaparin |  | Filtered heparin |
| Epinephrine |  | Catecholamine |
| Eptifibatide |  | Snake spit (Southeastern Pygmy Rattlesnake) |
| Etanercept |  | Recombinant antibody fragment |
| Factor IX complex |  | Pooled human plasma |
| Glucagon |  | Natural hormone |
| Guaifenesin |  | Extract of the ***Guaiacum*** trees |
| Heparin |  | Highly sulfated glycosaminoglycan of natural orgin |
| Hyaluronic acid |  | A glycosaminoglycan from bovine eye & rooster combs |
| Hydrocodone |  | Semi-synthetic opioid |
| Isotretinoin |  | Retinoid related to vitamin A |
| L-Dopa (levodopa) |  | Precursor of dopamine |
| Levothyroxine |  | Synthetic form of Thyroid hormone (T4) |
| Lidocaine |  | Based on chemicals found in mutant strains of barley |
| Lincomycin |  | From the soil actinomycete ***Streptomyces lincolnensis*** |
| Liraglutide |  | Gila monster spit |
| Lithium |  | Mineral |
| Mefloquine |  | Related to quinine from the cinchona tree of S. America |
| Melatonin |  | Synthetic form of melatonin |
| Metformin |  | Produced from two chemicals (guanidine and galegine) extracted from the plant “goat’s rue,” ***Galega officinalis***. |
| Metronidazole |  | A synthetic derivative of extracts from ***Streptomyces*** spp. |
| Misoprostol |  | Synthetic prostaglandin based on PGE1 |
| Morphine |  | Opium poppy |
| Naltrexone |  | Semi-synthetic opioid (antagonist) |
| Nesiritide |  | Recombinant form of a natriuretic peptide |
| Norepinephrine |  | Catecholamine |
| Pancrelipase |  | Digestive enzymes |
| Pilocarpine |  | Leaves of ***Pilocarpus*** plants |
| Prednisone |  | The bacteria ***Corynebacterium simplex*** is used to oxidize cortisone, the natural corticosteroid hormone |
| Pseudoephedrine |  | Based on ephedrine from the ***Ephedraceae*** family of plants. |
| Rasburicase |  | Recombinant urate oxidase |
| Rifampin |  | Chemically modified rifamycin, metabolites of the fungi ***Nocardia mediterranei***. |
| Scopolamine (aka hyoscine) |  | ***Atropa belladonna*** (deadly nightshade) and other plants in the ***Solanaceae*** family |
| Tinidazole |  | A synthetic derivative of extracts from ***Streptomyces*** spp. |
| Valproic acid (Divalproex) |  | An analogue of valeric acid found in valerian plants |
| Vancomycin |  | Isolated from soils in the jungles of Boneo containing the fungus ***Streptomyces orientalis*** |
| Vasopressin |  | Synthetic form of Antidiuretic Hormone (ADH) |
| Warfarin |  | A synthetic derivative of dicoumarol produced from a plant coumarin metabolized by a fungus infecting sweet clover. Dicoumarol = 2 coumarins. |

Additional resources (just FYI):

1. [*A Bitter Pill*](http://www.conservationmagazine.org/2012/03/a-bitter-pill/)*,* Richard Conniff. Conservation Magazine 2012 13(1):18-23. University of Washington.
2. [*A bitter pill in an anti-biotic world*](http://www.timeshighereducation.co.uk/books/a-bitter-pill-in-an-anti-biotic-world/162314.article)*,* Times Higher Education 17 June 1996. Review of:
   1. *Biodiversity Conservation – Problems and Policies*, Perrings, et. al. Editors. Springer. 1995.
3. [*Natural Products: Not the best fit for drugs*](http://pipeline.corante.com/archives/2010/07/12/natural_products_not_the_best_fit_for_drugs.php)? Derek Lowe blogging in the Corante Weblog a review of: [*Distinct Biological Network Properties between the Targets of Natural Products and Disease Genes*.](http://pubs.acs.org/doi/pdf/10.1021/ja102798t)  Dancik, et. al. J. Am. Chem. Soc. 2010, 132(27):9259-9261. (The review is short and easy to read, the scientific paper is very interesting and short, too).
4. [*Recent natural products based drug development: A pharmaceutical industry perspective*.](http://www.chem.uwec.edu/chem491_w01/%20Pharmacognosy%20491/Chem491-Medicianl%20Chem%202008/%20%20%20%20%20Med%20Chem%20Lectures/Lecture%20%206/reviewofnatProductPharm.pdf) Yue-Zhong Shu. J. Nat. Prod. 1998, 61:1053-1071. A good, if old, review of the field. Interesting, but long.
5. [*Strategies for discovering drugs from previously unexplored natural products*](http://www.ibmb.uni.wroc.pl/prace2/praca18.pdf). Alan Harvey. Drug Discovery Today. 2000. 5(7):294-300. Very interesting, a bit dated, but he presents some very provocative arguments.
6. Take a peek at some potential alternative career paths by exploring the links at the highly respected journal Nature. This [LINK](http://www.nature.com/drugdisc/nj/nj_dd_arch.html) takes you to their drug discovery careers archive – very interesting!