S-6 [15:00~15:30]

New Arylsulfonylimidazolidinones as Hypoxia Selective Anticancer Agent

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Recent biological studies have exploited many fundamental differences existing between tumor and normal tissues. The most conspicuous of these differences is the inefficient vasculature within solid tumor. In the normal tissue the balance between O2 supply and consumption is very well regulated and can be modulated by changes in blood flow and cellular O2 utilization. In contrast, in malignant tumors perfusion is poor and regulatory mechanisms are incomplete due to functional abnormalities resulting from altered morphology, altered rheology, and increased permeability1. As a result, areas with very low oxygen partial pressure exist in solid tumors, occurring either acute or chronic tumor hypoxia2. These oxygen deficient microregions are heterogeneously distributed within the tumor mass. In the normal tissue median pO2 values can vary from 24 to 66 mmHg, whereas median values in tumors can be as low as 5 mmHg, with high proportion of measurements being below 2.5 mmHg on the measurement made by polarographic needle electrode assay3. In hypoxic cells, enhanced resistance to radiation and chemotherapeutic agents has been well demonstrated4. Hypoxic cells are 3-fold more resistant to radiation than aerobic cells. Generally, hypoxic cells are noncycling due to a lack of nutrients and oxygen. The distance of such cells (more than 150 μ m away) from the nearest blood vessels and the increasing extravascular pressure inside tumor also make it difficult to deliver adequate drug concentration to the hypoxic regions by diffusion5. Although these factors make the hypoxic cells in solid tumors particularly resistant to conventional anticancer agents, at the same time the hypoxic microenvironment offers an attractive target. Tumor hypoxia generates very much-enhanced reductive and diminished oxidative environment as well as acidosis. Surprisingly many tumors with high vascular density have more severe hypoxic region than those with low vessel density4. These properties provide solid rationale for design of a prodrug, which can be selectively activated in hypoxic tumor. These types of drugs have been characterized as Hypoxia Selective Cytotoxin (HSC). In almost all HSCs studied to date, the activation process has been bioreductive one. To be effective in vivo, HSCs need to have relatively nontoxic

prodrug forms, which are not subject to rapid metabolism and are capable of efficient extravascular distribution. HSCs need to undergo rapid and selective metabolism in hypoxic environments. Selectivity is normally achieved by utilizing a reductive mechanism that occurs in all cell but that is reversible by molecular oxygen in normal tissue (Figure 1).

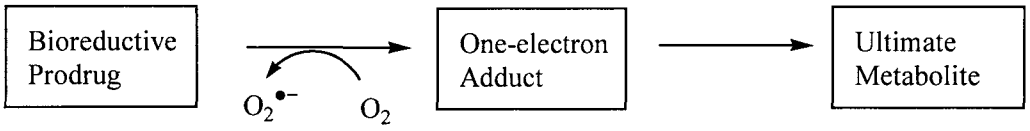


Figure 1. The generalized activation process for all bioreductive prodrug

Three hypoxia selective cytotoxins, such as mitomycin C, porfiromycin, and tirapazamine are introduced in clinical use. In 1980, nitrobenzyl compounds bearing efficient leaving group such as carbamate and halides show modest hypoxic selectivity in cell culture6. Their mechanisms of action are postulated to proceed through the formation of reactive quinoneimine mthides (**3**), which act as an alkylating agent to kill tumor cell. Later this type of mechanism was demonstrated with halogenomethylquinones7. In the initial step, electron withdrawing nitro group was easily reduced to amino group in hypoxic condition, which donate electron to the ring to accelerate departure of leaving group and eventually form a very reactive cytotoxic quinoneimine methides (**3**).

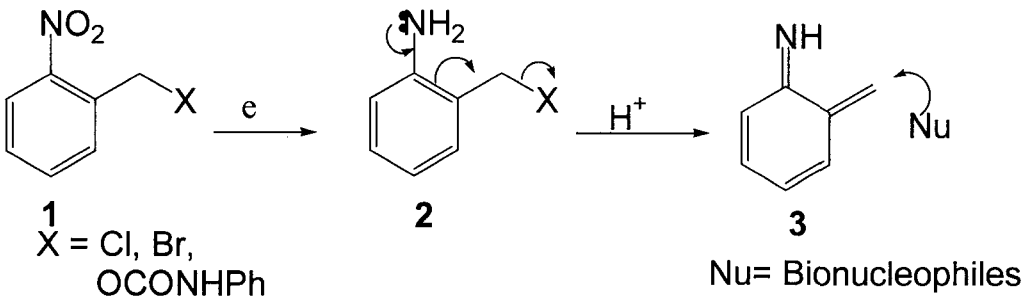
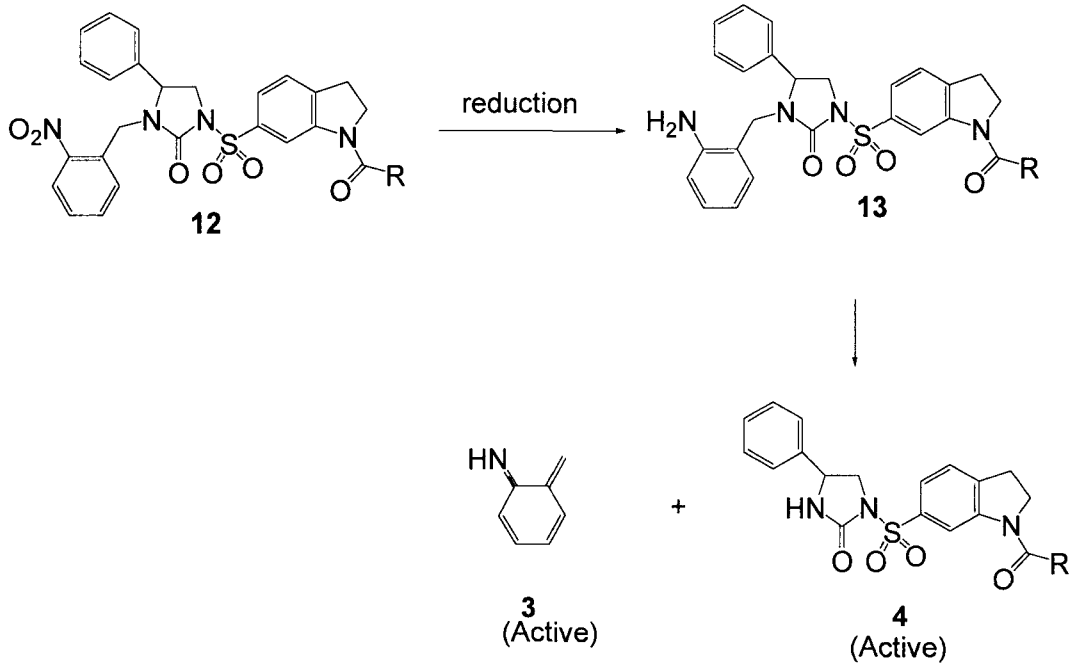


Figure 2. Postulated bioreductive alkylation of nitrobenzyl compounds

We took this concept to apply for prodrug design of antitumor arylsulfonylimidazolidinones (**4**) and arylsulfonylimidazolidinthiones (**5**) to be HSC. In our laboratory, very broad and effective activity of arylsulfonylimidazolidinones against human solid tumors have been demonstrated in at least 0.1 μ M level of GI50 values8. However the activities of these

In order to find the potential of these compounds to accomplish selective hypoxic cell kill, their cytotoxicities were measured against AA8 tumor cell under aerobic and hypoxic condition (<2% O_2) in vitro. Cytotoxicities were calculated range from 0.1 to 30 μ g/mL as GI50. With this limitation selectivity were calculated. Family of **6** and **7** show comparable selectivity to mitomycin C. Most selective compound shows selectivity more than 20. Compound **8** and **9** have rather low selectivity. Therefore we believe some of these compounds have the potential to be HSC. The preliminary feature of arylsulfonylimidazolidinones as HSC will be discussed.

Figure 5, Postulated hypoxia activation of target molecule



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