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Click chemistry inspired facile synthesis and bioevaluation of novel triazolyl analogs of Ludartin ☆

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ABSTRACT

A convenient and modular synthesis involving diastereoselective Michael addition followed by regioselective Huisgen 1,3-dipolar cycloaddition reaction was carried out to furnish 1,4-disubstituted-1,2,3-triazoles of Ludartin. This reaction scheme involving Michael addition followed by regioselective Huisgen 1,3-dipolar cycloaddition reaction leading to the formation of triazolyl analogs is being reported for the first time. All the triazolyl products were characterised using spectral data analysis. Sulphorhodamine B cytotoxicity screening of the resulting products against a panel of five human cancerous cell-lines revealed that few of the analogs display promising broad spectrum cytotoxic effect. Among all the synthesized compounds, only **3q** displayed the best cytotoxic effect with IC_{50} values of 12, 11, 38, 39 and 8.5 μM but less than the standard Ludartin (**1**) with IC_{50} values of 6.3, 7.4, 7.5, 6.9 and 0.5 μM against human neuroblastoma (T98G), lung (A-549), prostate (PC-3), colon (HCT-116) and breast (MCF-7) cancer cell lines, respectively. The present synthesis was designed based on the previous literature reports of Ludartin as an aromatase inhibitor. Our work provides an initial study on structure–activity relationship of triazolyl analogs of sesquiterpene lactones in general and Ludartin (**1**) in particular.

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Sesquiterpene lactones (SLs) form one of the largest biogenetically homogenous group of secondary metabolites known. SLs have been a subject of vast number of phytochemical/biological studies in the past four decades, mainly due to the fact that many of them display various conspicious biological activities.[1–3] These biological activities are attributed to the presence of electrophilic structure elements in SLs which undergo covalent reaction with functional biological molecules resulting in their deactivation.[1–3] The alkylation of free sulphur moieties of enzymes and other functional proteins by SLs is responsible for SL bioactivity.[1–3] This is in harmony with the pearsons hard-soft acid base principle (HSAB) that soft nucleophiles and electrophiles react more readily with each other than with reactants classified as hard electrophiles and nucleophiles, for example, non-conjugated carbonyl groups and amino or hydroxyl groups, respectively.[4,5]

Among the sesquiterpene lactones only a few have reached clinical trials which include artemisinin from *Artemisia annua* L, thapsigargin from *Thapsia garganica* and parthenolide from *Tanacetum parthenum*.[6] However owing to the relatively non selective mechanism of action, most of the SLs are not suitable for drug development. To address this non specificity issue amino prodrug approach has been developed to improve their pharmacokinetic potential.[7] Following the amino prodrug approach effective structure–activity relationships have been developed for various guaianolides (Fig. 1A) including, Ludartin[8] (**1**), arglabin[9] and other non-guaianolide sesquiterpene lactones (Fig. 1B) like alantolactone,[10] isoalantolactone,[10] costunolide,[11] parthenolide,[12–15] α-santonin,[16] helenalin[17] and ambrosin.[18] As a result few synthetic derivatives which include (11*R*)-13-(dimethyl-amine)-11,13-dihydroarglabin and (11*R*)-13-(dimethyl amine)-11,13-dihydroparthenolide have reached to clinical trials.[6,9]

Arglabin along with its dimethylamine analog, (11*R*)-13-(dimethylamine)-11,13-dihydroarglabin is an approved anticancer agent in several countries for treatment of lung, liver, breast and ovarian cancers. [9] (11*R*)-13-(dimethylamine)-11,13-dihydro-arglabin has less side effects than other chemotherapeutic agents.[9]

Ludartin (**1**), position isomer of Arglabin, shows gastric cytoprotective effect[19] and also inhibits aromatase enzyme which is involved in hormone-dependent breast cancer.[20,21] Earlier, we reported the structure–activity relationship of amino analogs of Ludartin (**1**) at its highly reactive α-methylene-γ-lactone moiety.[8] Some of the amino derivatives of Ludartin (**1**) were found to be potent and selective cytotoxic agents and the results were in fine tune with those reported for Arglabin by *R. Csuk* and coworkers that the Michael addition at the exocyclic double bond leads to derivatives with reduced/or equal cytotoxic effect but cell line

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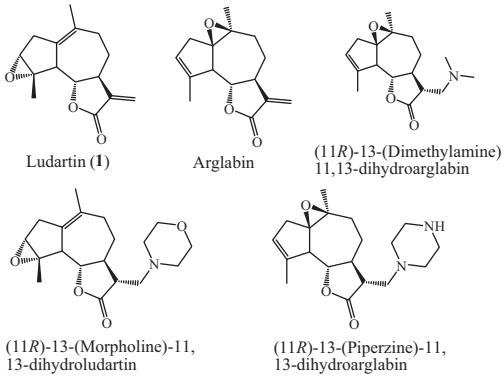


Figure 1A. Some bioactive guaianolides that have been studied for SAR and their active analogs.

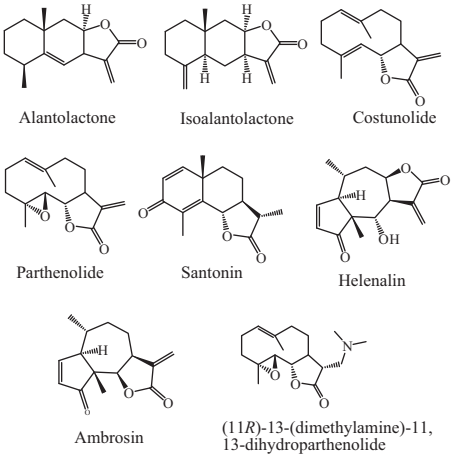


Figure 1B. Some bioactive Sesquiterpene lactones apart from guaianolides.

dependent selectivity.[9] Keeping in view the fact that Ludartin inhibits aromatase enzyme involved in hormone-dependent breast cancer and that the triazole based aromatase inhibitors in general represent the third generation frontline therapy for early and even advanced cases of breast cancer in postmenopausal women[21], we designed a reaction strategy, to develop effective triazole based analogs to rationalise lead properties of Ludartin (**1**) especially against breast cancers, involving a combination of Michael addition and Huisgen 1,3-dipolar cycloaddition reaction.

In view of the broad spectrum cytotoxic potential of triazoles in general, the triazole analogs of Ludartin were screened against other cancer cell-lines available, apart from breast cancer cells (MCF-7). An exhaustive literature survey revealed that such triazolyl formation has not been reported on any sesquiterpene lactone so far using click chemistry approach and represents the first of its kind on any sesquiterpene lactone and thus constitutes an initial structure–activity relationship of triazolyl derivatives of sesquiterpene lactone class of natural products in general and Ludartin (**1**) in particular.

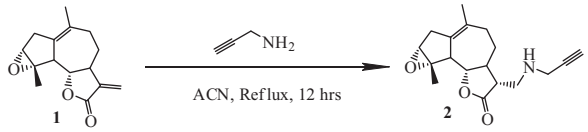
Ludartin (**1**) was subjected to Michael addition using propargyl amine in acetonitrile under reflux at its highly reactive α-methylene-γ-lactone motif described previously (Scheme 1A).

This reaction serves two important purposes: one it gives adducts that react in a *retro*-michael's fashion at the target site as is hypothesized for amino analogs of sesquiterpene lactones[8] and simultaneously acts as a template (terminal triple bond) for the second step of the reaction. Formation of propargylated product (**2**) in the first step could easily be confirmed by the disappearance of two diagnostic proton resonances at δ 5.38 ppm (d, J = 3.5 Hz) and δ 6.21 ppm (d, J = 3.5 Hz) of α-methylene-protons (13-H_2) of Ludartin (**1**).

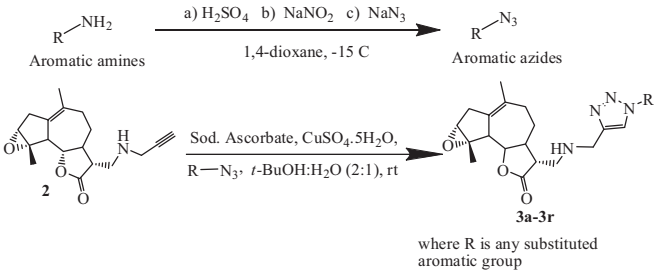
Such reaction creates one more chiral center at C-11 position whose configuration was determined as *R* on the basis of correlations deduced from NOESY described earlier.[8] On the other hand aromatic azides were prepared from their corresponding aromatic amines by diazotisation with sodium nitrite in acidic conditions followed by displacement with sodium azide. These aromatic azides were allowed to undergo 1, 3-dipolar cycloaddition reaction typically called Huisgen cycloaddition with the terminal acetylene bearing Michael adduct (**2**) under sharpless click chemistry conditions ($CuSO_4{\cdot}5H_2O$ and sodium ascorbate in *t*-BuOH/H_2O (2:1)) to afford regioselectively 1,4-disubstituted-1,2,3-triazoles in good to excellent yields[22] (Scheme 1B, Table 1). Under these conditions a series of such analogs was synthesized to look for structure–activity relationship studies. All the triazolyl products were characterised using spectral data analysis. Formation of products could easily be confirmed by a very down field *H*-5 proton signal (almost around 8.0 Hz) and other proton resonances in the aromatic region. Further characterisation of the products was done using ^{13}C, DEPT-NMR and HRMS as well as ESI-MS.

Ludartin (**1**) and its triazolyl analogs were then studied in a colorimetric Sulphorhodamine B (SRB) cytotoxicity assay[23] against a panel of five human cancer cell lines viz. neuroblastoma (T98G), lung (A-549), prostate (PC-3), colon (HCT-116) and breast (MCF-7). Preliminary cytotoxicity screening of the analogs was carried out at 50 μM concentration and cell death was determined. Ludartin (**1**) served as a positive control in this assay. The analogs which exhibited significant cytotoxic effect, greater than 50% growth inhibition at the preliminary screening concentration were further assayed at different concentrations (5–50 μM) to generate the IC_{50} values given in Table 2. The values are the average of the triplicate analysis.

From the cytotoxicity profile it is clear that the parent molecule, Ludartin (**1**) demonstrated to be cytotoxic not only against human leukaemia (THP -1), lung (A-549), colon (HCT-116), and prostate (PC-3) as described earlier[8] but proved to be effectively cytotoxic against breast (MCF-7) and neuroblastoma (T98G) cancer cells with IC_{50} values of 0.5 and 6.3 μM respectively. Among the synthesized triazolyl analogs, only five compounds **3a**, **3d**, **3e**, **3q** and **3r** exerted broad spectrum cytotoxic effects against the tested cancer cell-lines at their preliminary screening concentration (50 μM) and hence IC_{50} values of these analogs were evaluated. Compound **3q**



Scheme 1A. Preparation of amino propargyl of Ludartin.[8]



Scheme 1B. Preparation of aromatic azides and the triazoles of **2**.

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