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MOLECULAR DESIGN, CHEMICAL SYNTHESIS AND BIOLOGICAL STUDIES OF NOVEL ENEDIYNES RELATED TO DYNEMICIN A

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Abstract: Two novel enediynes **1** and **2** and related molecules containing a (Z)-7-sulfonyl-3-hepten-1,5-diyne functionality and quinoline moiety related to dynemicin A were synthesized from quinoline and 4-methoxyquinoline, respectively. The key synthetic features involve (1) magnesium acetylide addition to the 1-acylsalt of the quinolines (2) a Pd(0)-Cu(I) catalyzed coupling reaction of vinyl chloride or aryl iodide with acetylenes (3) conversion of the alcohol to a sulfide, followed by oxidation to a sulfone. These molecules proved to be active against the growth of leukemia, colon, epidermoid and melanoma cancer cell lines.

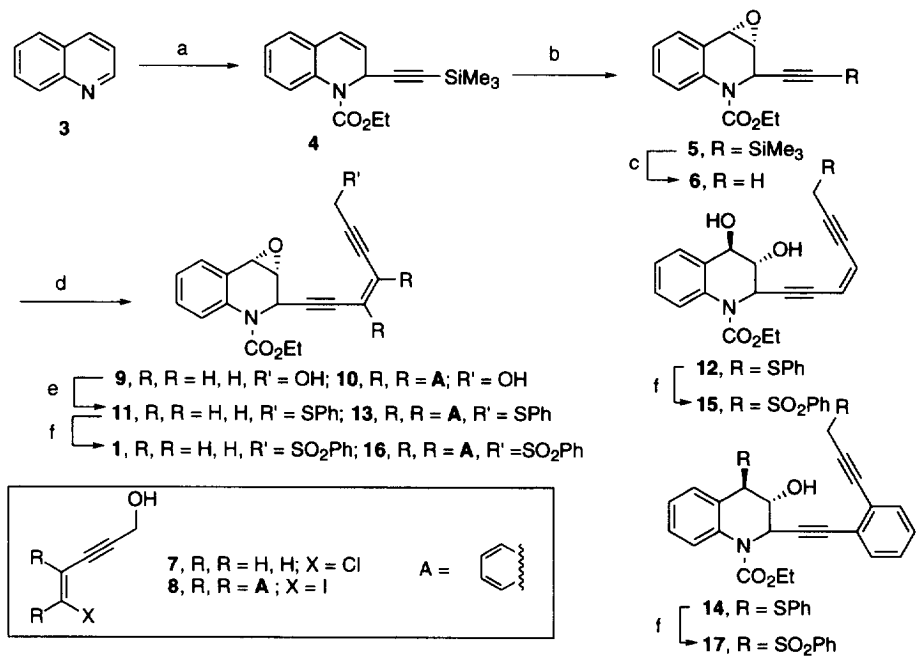
The enediyne antitumor antibiotics, represented by neocarzinostatin,[1] the calicheamicins,[2] esperamicins,[3] and dynemicins,[4] have attracted much attention due to their unusual molecular architecture and mode of activation leading to the formation of benzenoid diradicals and the resulting cleavage of DNA. In addition to the synthesis of the natural products, considerable efforts have been made to the development of new, simple and stable analogs which mimic their chemistry and biological action.[5] In a prototypical, Myers reported the cyclization of allene-eneynes to form α,3-didehydrotoluene radicals.[6] Based on the Myers cyclization, various allene-eneyne containing molecules have been synthesized and tested to investigate their ability to cleave DNA.[7] Recently, we described a simple molecule containing a (Z)-7-sulfonyl-3-hepten-1,5-diyne functionality which undergoes Myers cyclization to form a biradical under alkaline conditions and which exhibits the ability to cleave DNA.[8] In order to search for more potent anticancer drugs, we have investigated the design, synthesis and activities of novel enediynes containing the sulfone-enediyne system and quinoline moiety related to dynemicin A.

These acyclic enediyne-sulfone systems (**1** and **2**) are expected to have the following distinctive features: (1) the acyclic enediyne structure is stable at ambient temperature[9]; (2) the enediyne sulfone can be converted to an enyne-allene system which would rapidly cyclize to form a diradical upon treatment with base; (3) the quinoline core related to dynemicin A can deliver the molecule to DNA, and the epoxide of **1** and keto group of **2** can form a hydrogen bond with a specific site of DNA. These features would then mimic the biological action of the naturally occuring enediyne molecules.

The synthesis of **1** and analogs is summarized in Scheme I. Addition of the Grignard reagent, derived by the reaction of ethyl magnesium chloride with trimethylsilylacetylene, to 1-acyl quinolinium salt **3** gave dihydroquinoline **4** in 52% yield.[10] Oxidation of **4** with *meta*-chloroperbenzoic acid (mCPBA) afforded epoxide **5** in 82% yield. Compound **5** was desilylated using tetrabutylammonium fluoride (TBAF) in THF to give acetylene **6** in 94% yield. Cross-coupling reactions of **6** with vinyl chloride **7** and phenyl iodide **8** using $Pd(PPh_3)_4$ and CuI as catalysts in the presence of butylamine in ether gave enediyne alcohols **9** (40%) and **10** (56%), respectively. The resulting alcohol (**9**), was converted to the corresponding mesylate by the standard

method (MsCl, Et_3N in CH_2Cl_2). Subsequent reaction of the mesylate with thiophenol under alkaline conditions (NaOH in aqueous THF) afforded sulfide **11** (7%) along with the dihydroxy sulfide **12** (28%). Alcohol **10** was converted to **13** (5%) and **14** (11%) under the same reaction conditions. Sulfides **11**, **12**, **13** and **14** were oxidized with mCPBA to afford the corresponding sulfones **1** (57%), **15** (74%), **16** (81%) and **17** (62%), respectively.

Scheme I[a]



[a]**Reagents and conditions**: (a) EtMgCl. $HCCSi(CH_3)_3$, THF, 1 h, then **3**, $ClCO_2Et$, THF, 25 °C, 2h, 52%; (b) mCPBA, CH_2Cl_2, 1.5 h, 82%; (c) TBAF, THF, 10 min, 94%; (d) **7** or **8**, $Pd(PPh_3)_4$, CuI, $BuNH_2$, Et_2O, 25 °C, 6 h (e) (i) MsCl, Et_3N, CH_2Cl_2, 25 °C, 2 h; (ii) HSPh, NaOH, THF-H_2O, 1 h; (f) mCPBA, CH_2Cl_2, 30 min.

Compound **2** and analogs were synthesized in a similar manner starting from 4-methoxyquinoline (**18**)[11] as outlined in Scheme II. Reaction of the 1-acyl salt of 4-methoxyquinoline with the Grignard reagent, derived from trimethylsilylacetylene and ethylmagnesium chloride, followed by hydrolysis of the resulting dihydroqunoline (**19**) with 1N HCl gave ketone **20** in 92% yield. Desilylation of **20** using TBAF in THF,[12] or Na_2CO_3 in methanol,[13] afforded acetylene **21** in 93% and 85% yields, respectively. The cross-coupling reactions of **21** with vinyl chloride **7** and phenyl iodide **8** using $Pd(PPh_3)_4$ as a catalyst afforded enediyne alcohols **22** (52%) and **23** (70%), respectively. Alcohol **22** was converted to sulfide **24** in 80% yield by the procedure described above. Alcohol **23** was converted to **25** (70%) under the same reaction conditions. Finally, sulfides **24** and **25** were oxidized with mCPBA to afford sulfones **2** (93%) and **26** (75%), respectively.

The activities of compounds **1**, **2**, **6**, **15**, **16**, **17** and **26** were evaluated *in vitro* against four human tumor cell lines (colo 205, Hep G2, SK-BR-3 and Molt-4). For each compound, dose response curves for each cell line

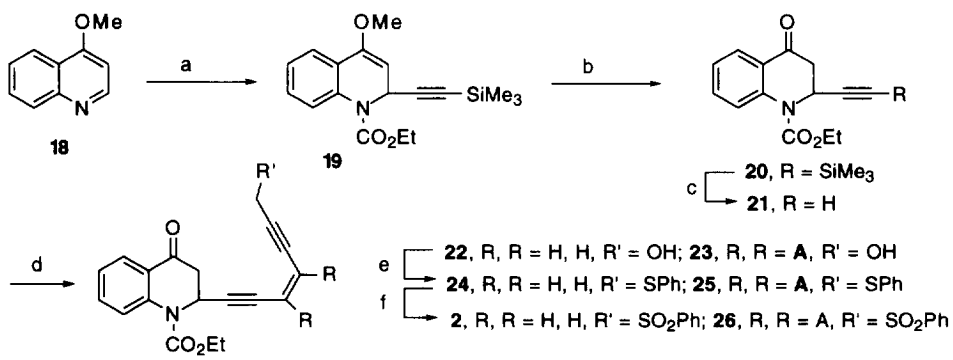
were measured at five different drug concentrations. The concentrations causing 50% cell growth inhibition (IC_{50}) compared with the control were calculated, and the results are summarized in Table 1. The phenyl 1,2-bisacetylene analogs **16** and **17** proved to be active against the growth of leukemia (Molt-4), colon (colo 205), epidermoid (Hep G2) and melanoma (SK-BR-3) cancer cell lines. Enediynes **1** and **15** and keto analogs **2** and **26** showed lower potency against these cell lines. Compound **6** lacking the enediyne moiety proved to be inactive against the growth of these four cancer cell lines.

Table 1. Inhibition of *in vitro* Human Tumor Cell Growth by **1**, **2**, **6**, **15**, **16**, **17** and **26** (IC_{50}, μg/mL)[a]

compound	Hep G2[b]	Colo 205	SK-BR-3	Molt-4
1	9.01	25.97	19.47	5.50
2	50.21	53.04	43.87	5.63
6	>100	>100	>100	66.54
15	57.81	49.74	46.71	10.18
16	8.91	9.59	9.23	4.64
17	3.75	5.33	6.26	0.73
26	70.00	50.12	53.64	7.26

[a]IC_{50} value are the concentrations corresponding to 50% growth inhibition. [b]Cell type: Hep G2, epidermoid cell line; Colo 205, colon cell line; SK-BR-3, melanoma cell line; Molt-4, leukemia cell line.

Scheme II[a]



[a]**Reagents and conditions**: (a) $EtMgCl$, $HCCSi(CH_3)_3$, then **18**, $ClCO_2Et$, THF, 25 °C, 2h, 92%; (b) 1N HCl, THF, 10 min, quant.; (c) TBAF, THF, 10 min, 93% or Na_2CO_3, CH_3OH, 1h, 85%; (d) **7** or **8**, $Pd(PPh_3)_4$, CuI, $BuNH_2$, Et_2O, 25 °C, 6h; (e) (i) MsCl, Et_3N, CH_2Cl_2; (ii) HSPh, NaOH, THF-H_2O, 1h; (f) mCPBA, CH_2Cl_2, 1h.

In conclusion, the (Z)-7-sulfonyl-3-hepten-1,5-diyne functionality is essential for formation of the diradical and antitumor activity. The introduction of a quinoline moiety into this system has little effect on the biological

activities. The synthesis of more potent and selective enediyne-sulfone containing anticancer drugs is under investigation.

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