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Acyclic enediynes fused to triazole and benzothiophene containing propargylamine moieties

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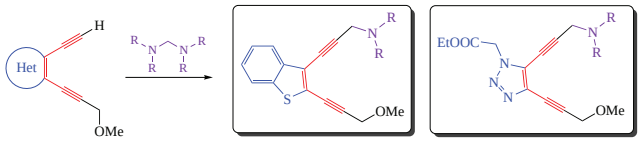
Synthesis of 3-(5-triazolyl)- and 3-(3-benzothienyl)-propargylamines includes the Mannich reaction of the corresponding ethynyl derivatives with diaminomethanes. The MTT test of the synthesized compounds toward the viability of NCI-H460 lung carcinoma cells and WI-26 VA4 normal lung fibroblast cells reveals one of them possessing a notable cytotoxic activity.



Keywords: enediynes, propargylamines, heterocycles, 1,2,3-triazoles, benzothiophene, Sonogashira reaction, Mannich reaction, cytotoxicity.

Since the discovery (the 1980s) of the first enediyne antibiotics and determination of their mode of action, enediynes have emerged as a promising class of cytostatic antibiotics.[1–7] Enediyne with (*Z*)-3-en-1,5-diyne moiety are able to undergo thermal cycloaromatization (the Bergman cyclization)[8–10] leading to the formation of diradicals that determines the mechanism of biological activity of enediynes [Figure 1(*a*)].[11]

An alternative pathway is the Myers–Saito cyclization[12–14] of the corresponding enyne-allenes [Figure 1(*c*)]. Due to the instability of natural enediynes, low selectivity of their action and side effects,[15] only a few anticancer drugs are presented today on the pharmaceutical market, namely, based on *N*-acetyl calicheamicin γ_1^I are gemtuzumab ozogamicin (Mylotarg®)[16] and inotuzumab ozogamicin (Besponsa®) [see Figure 1(*b*)],[17] while based on the

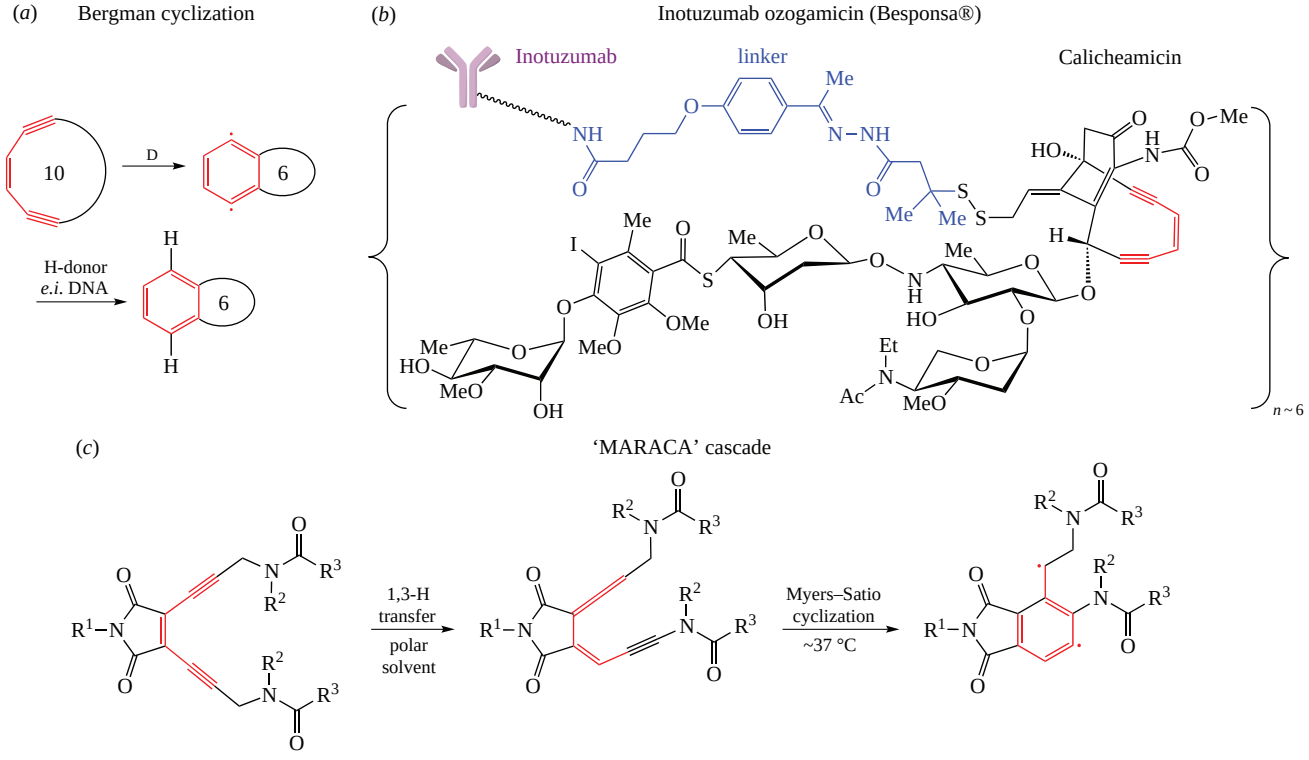
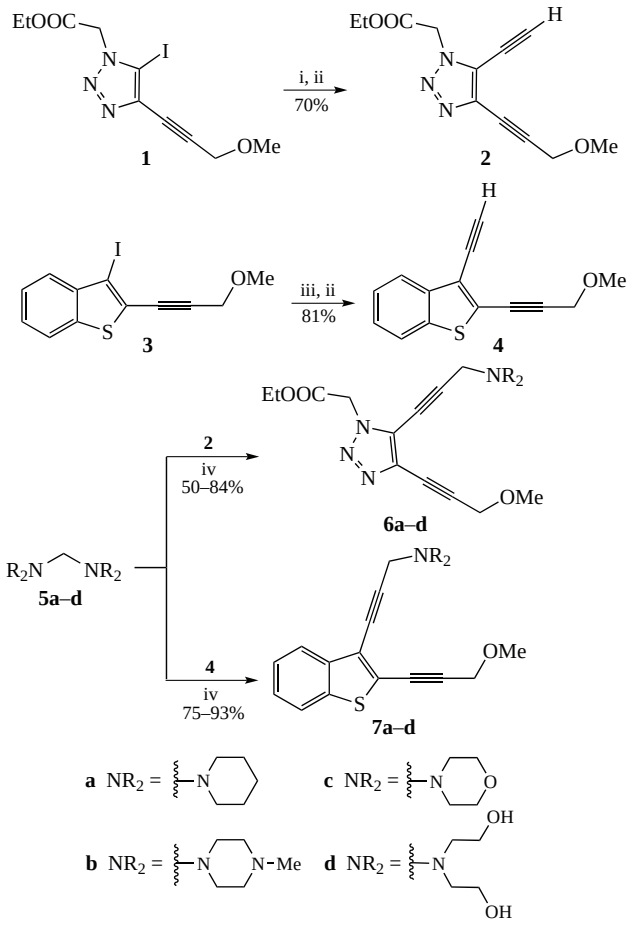


Figure 1 (*a*) General mechanism of action of enediyne antibiotics, (*b*) structure of the enediyne containing the approved drug inotuzumab ozogamicin (Besponsa®) and (*c*) maleimide-assisted rearrangement and cycloaromatization (MARACA) of acyclic analogs of enediyne.

chromophore of neocarsinostatin is zinostatin stimalamer (SMANCS). In this regard, the design and synthesis of simpler enediyne molecules remains an urgent task, both for studying the factors controlling the formation of the key diradical intermediates, and for developing new anticancer agents to improve the selectivity of the enediyne cytotoxic effect and to overcome other limitations associated with natural compounds.[18,19]

Our research in this area has been focused on molecular design, synthesis, and structure–property relationship of 10-membered heteroenediynes fused to heterocycles.[20,21] As for more accessible acyclic enediynes, they were not considered as antitumor agents, since they usually are not active in the Bergman cyclization under physiological conditions. However, recently it was reported that acyclic symmetrical substituted enediynes fused to a maleimide moiety were able to generate a diradical at room temperature and exhibited high cytotoxicity against various cancer cell lines.[22–26] It was found that the maleimide fragment promoted isomerization of enediynes into enyne-allenes; as a result, the Myers–Saito cyclization mechanism was triggered. One of the acyclic enediynes that showed high activity was a compound containing propargylamine fragments.[23]

In this work, in order to expand the number of acyclic enediynes conjugated with five-membered heterocycles such as 1,2,3-1*H*–triazole and benzothiophene, asymmetrically substituted acyclic enediynes containing propargyl and propargylamine substituents were synthesized (Scheme 1) and their cytotoxicity towards cancer and normal cells was studied.



Scheme 1 *Reagents and conditions:* i, $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, K_3PO_4, THF, 65 °C; ii, KF, DMF/H_2O (10 : 1), room temperature; iii, $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, DIPA, DMF, 40 °C; iv, $CH_2(NR_2)_2$ **5a–d**, CuCl, dioxane, 50–80 °C.

Table 1 Cytotoxic effects of compounds **7a**,**b** on the cancer and normal human cell lines.

Compound	IC_{50} (μM) values	
	Cancer line NCI-H460	Normal line WI-26VA
7a	20.7 ± 3.76	24.6 ± 1.9
7b	n.d.	24.9 ± 2.5
etoposide	0.98 ± 0.33	0.42 ± 0.25

Over the past few years, a rapid growth of interest towards propargylamine derivatives was observed.[27] The classical method for obtaining such compounds is the Mannich reaction which involves three components such as terminal alkyne, formaldehyde (generated *in situ* from paraformaldehyde) and secondary amine called the A^3-coupling reaction.[28] This method has a specific place because of its convenience/atom efficiency.[29] Diaminomethanes used for this purpose require sufficiently mild conditions and the use of catalytic amounts of metal salts thus avoiding the formation of by-products.[30–32]

As the key compounds, we used terminal acetylenes **2** and **4**, which were synthesized from TMS-substituted internal alkynes obtained by the Sonogashira reaction of TMS-acetylene with 5-iodo-1,2,3-triazole **1** and 3-iodobenzothiophene **3**, respectively (see Scheme 1). Subsequent removal of the trimethylsilyl group was carried out with potassium fluoride in the DMF/water system (10 : 1). The starting 5-iodo-1,2,3-triazole **1**[33] and 3-iodobenzothiophene **3**[34] were obtained according to the previously reported procedures.

For the preparation of propargylamines, we have chosen a modification in which pre-synthesized diaminomethanes **5a–d** obtained from secondary amines and paraformaldehyde were used. The reaction of terminal acetylenes **2** and **4** with diamino-methanes **5a–d** was carried out in the presence of CuCl under argon atmosphere with the formation of the corresponding Mannich bases **6a–d** and **7a–d**.

For all synthesized acyclic enediynes **6a–d** and **7a–d**, the effect on the proliferation of lung carcinoma cells NCI-H460 and lung fibroblasts WI-26VA4 was evaluated using the MTT colorimetric test.[35] Etoposide with the cytotoxic effect associated with an inhibitory effect on topoisomerase II[36] was utilized as a reference drug in cellular experiments. Acyclic enediynes based on 1,2,3-triazole **6a–d** have no cytotoxic effect at a 50 mmol dm^{-3} concentration on tumor (NCI-H460) and normal cell lines (WI-26 VA4). In contrast, among the benzothiophene derivatives, compound **7a** demonstrated notable cytotoxicity against cancer cells (Table 1). At the same time, compounds **7a**,**b** have also affected normal WI-26VA4 cells. The benzothiophene derivatives **7c**,**d** showed no significant antiproliferative effect.

In conclusion, the developed synthetic approach opens access to a variety of acyclic enediynes containing propargylamine substituents.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.04.010.

References

1 M. Konishi, H. Ohkuma, K-I. Saitoh, H. Kawaguchi, J. Golik, G. Dubay, G. Groenewold, B. Krishnan and T. W. Doyle, *J. Antibiot.*, 1985, **38**, 1605.
2 B. Shen, Hindra, X. Yan, T. Huang, H. Ge, D. Yang, Q. Teng, J. D. Rudolf and J. R. Lohman, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 9.
3 M. Igarashi, R. Sawa, M. Umekita, M. Hatano, R. Arisaka, C. Hayashi, Y. Ishizaki, M. Suzuki and C. Kato, *J. Antibiot.*, 2021, **74**, 291.
4 S. Lavy, A. Pérez-Luna and E. Kündig, *Synlett*, 2008, 2621.
5 M. Jean, S. Tomasi and P. van de Weghe, *Org. Biomol. Chem.*, 2012, **10**, 7453.
6 M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Siegel, G. O. Morton, W. J. McGahren and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3466.
7 M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3464.
8 R. R. Jones and R. G. Bergman, *J. Am. Chem. Soc.*, 1972, **94**, 660.
9 P. R. Hamann, J. Upeslacis and D. B. Borders, *Anticancer Agents from Natural Products*, eds. G. M. Cragg, D. G. I. Kingston and D. J. Newman, CRC Press, Boca Raton, FL, USA, 2011.
10 J. J. Li, in *Name Reactions*, Springer, Cham, 2021, pp. 166–175.
11 J. P. Cosgrove and P. C. Dedon, in *Small Molecule DNA and RNA Binders*: *From Synthesis to Nucleic Acid Complexes*, eds. M. Demeunynck, C. Bailly and W. D. Wilson, Wiley-VCH, Weinheim, 2004, vol. 2, pp. 609–642.
12 A. G. Myers, E. Y. Kuo and N. S. Finney, *J. Am. Chem. Soc.*, 1989, **111**, 8057.
13 A. G. Myers and P. S. Dragovich, *J. Am. Chem. Soc.*, 1989, **111**, 9130.
14 K. Saito, T. Watanabe and K. Takahashi, *Chem. Lett.*, 1989, **18**, 2099.
15 R.-G. Shao, *Curr. Mol. Pharmacol.*, 2010, **1**, 50.
16 C. D. Godwin, R. P. Gale and R. B. Walter, *Leukemia*, 2017, **31**, 1855.
17 Y. N. Lamb, *Drugs*, 2017, **77**, 1603.
18 P. Bhattacharya, A. Basak, A. Campbell and I. V. Alabugin, *Mol. Pharmacol.*, 2018, **15**, 768.
19 R. Romeo, S. V. Giofre and M. A. Chiacchio, *Curr. Med. Chem.*, 2017, **24**, 3433.
20 N. A. Danilkina, A. S. D'yachenko, A. I. Govdi, A. F. Khlebnikov, I. V. Kornyakov, S. Bräse and I. A. Balova, *J. Org. Chem.*, 2020, **85**, 9001.
21 N. A. Danilkina, E. A. Khmelevskaya, A. G. Lyapunova, A. S. D'yachenko, A. S. Bunev, R. E. Gasanov, M. A. Gureev and I. A. Balova, *Molecules*, 2022, **27**, 6071.
22 H. Chen, B. Li, M. Zhang, H. Lu, Y. Wang, W. Wang, Y. Ding and A. Hu, *ChemistrySelect*, 2020, **5**, 7069.
23 M. Zhang, H. Ma, B. Li, K. Sun, H. Lu, W. Wang, X. Cheng, X. Li, Y. Ding and A. Hu, *Asian J. Org. Chem.*, 2021, **10**, 1454.
24 M. Zhang, B. Li, H. Chen, H. Lu, H. Ma, X. Cheng, W. Wang, Y. Wang, Y. Ding and A. Hu, *J. Org. Chem.*, 2020, **85**, 9808.
25 M. Zhang, H. Lu, B. Li, H. Ma, W. Wang, X. Cheng, Y. Ding and A. Hu, *J. Org. Chem.*, 2021, **86**, 1549.
26 H. Lu, H. Ma, B. Li, M. Zhang, H. Chen, Y. Wang, X. Li, Y. Ding and A. Hu, *J. Mater. Chem. B*, 2020, **8**, 1971.
27 I. Jesin and G. C. Nandi, *Eur. J. Org. Chem.*, 2019, 2704.
28 C. Mannich and F. T. Chang, *Ber. Dtsch. Chem. Ges.*, 1933, **66**, 418.
29 Y. Volkova, S. Baranin and I. Zavarzin, *Adv. Synth. Catal.*, 2021, **363**, 40.
30 M. G. Shaibakova, I. G. Titova, A. G. Ibragimov and U. M. Dzhemilev, *Russ. J. Org. Chem.*, 2008, **44**, 1126 (*Zh. Org. Khim.*, 2008, **44**, 1141).
31 V. R. Akhmetova, N. S. Akhmadiev, G. M. Nurtdinova, V. M. Yanybin, A. B. Glazyrin and A. G. Ibragimov, *Russ. J. Gen. Chem.*, 2018, **88**, 1418 (*Zh. Obshch. Khim.*, 2018, **88**, 1126).
32 A. I. Govdi, I. V. Sorokina, D. S. Baev, A. O. Bryzgalov, T. G. Tolstikova, G. A. Tolstikov and S. F. Vasilevsky, *Russ. Chem. Bull.*, 2015, **64**, 1327.
33 A. I. Govdi, N. A. Danilkina, A. V. Ponomarev and I. A. Balova, *J. Org. Chem.*, 2019, **84**, 1925.
34 A. G. Lyapunova, N. A. Danilkina, A. M. Rumyantsev, A. F. Khlebnikov, M. V. Chislov, G. L. Starova, E. V. Sambuk, A. I. Govdi, S. Bräse and I. A. Balova, *J. Org. Chem.*, 2018, **83**, 2788.
35 T. Mosmann, *J. Immunol. Methods*, 1983, **65**, 55.
36 K. Hande, *Eur. J. Cancer*, 1998, **34**, 1514.

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