Anticancer Properties of newly synthesized 1,4-Napthoquinone Analogs.

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Project Overview

Between 1940 – 2004, 335 infectious diseases were reported.[1] It is estimated that three new diseases are being identified every couple of years and such trend is constantly increasing.[2] Not only the new diseases, but also the known infectious agents are able to develop resistance against available drugs through mutations or genetic exchange and evolve into new deadly strains. With the growing rate of bacterial infections and antibiotic resistance, there have been continuous calls for new antibacterial agents.

Our group is working on synthesis of cationic anthraquinone analogs, which contains a 1,4-Napthoquinone core, as antibacterial or anticancer agents. 1,4-Napthoquinone is ubiquitous in nature and display a wide range of biological activities. The quinine derivatives are of particular interest due to their redox inhibiting process of ubiquinone. By substituting different functional group, it is possible to tune the antibacterial and anticancer properties of those cationic anthraquinone analogs. Herein, we report the synthesis of new 1-aryl-1*H*-naphthol[2,3-d]triazole-4,9-diones and 1-alkyl-1*H*-naphthol[2,3-d]triazole-4,9-diones by [2+3] cycloaddition of corresponding substituted azide with 1,4-napthoquinone. These compounds are further converted to new member of cationic anthraquinone analogs via alkylation at N-3 position of the triazole.

These new compounds were evaluated for their biological activity against different strains of bacteria and cancer cell-lines. The result showed the compounds are not very effective against bacteria but very effective against some cancer cells. The detail synthetic route, general structure of the compound and biological activities against cancer cells are discussed here.

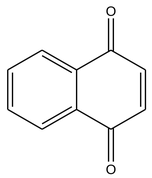


Figure 1: 1,4-napthoquinone.

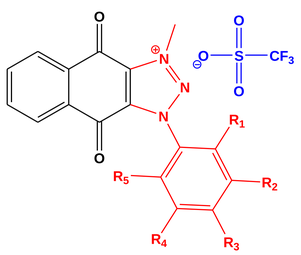
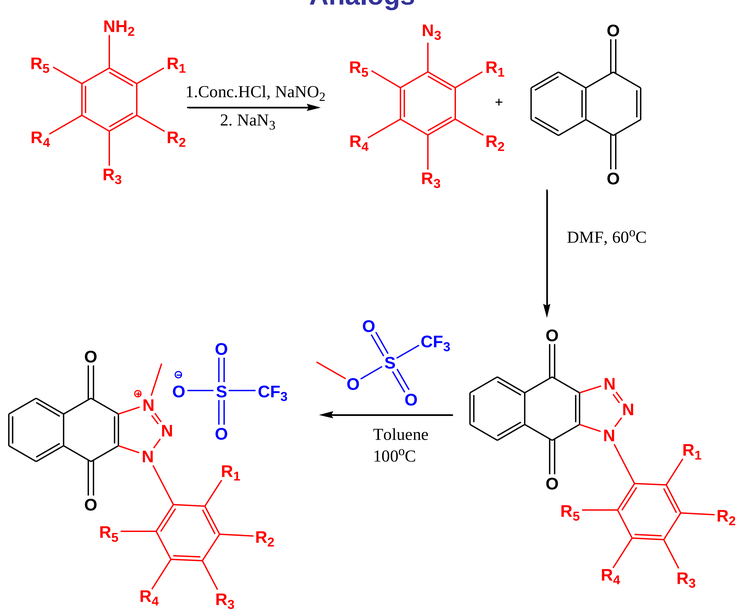


Figure 2: General structure of new 1,4-Napthoquinone analog. R_1, R_2, R_3, R_4, R_5 = Functional Group

Library of New 1,4-Napthoquinone Analogs

Phase 1		Phase 2	
Compound Code	**Functional Group**	**Compound**	**Functional Group**
NQM120	R_1, R_2, R_3, R_4, R_5= H	NQM 130	R_1, R_3,R_5 = H R_2, R_4 = EDG
NQM121, NQM124	R_1, R_2, R_3, R_4,R_5= H R_3 = EDG	NQM 131	R_1, R_5 = H R_2, R_3, R_4 = EDG
NQM122, NQM125 NQM127	R_1, R_2, R_3, R_4,R_5= H R_3 = EWG	NQM 132	R_1, R_4, R_5 = H R_2,R_3 = EDG

Reaction Scheme for Synthesis of Anthraquinone Analogs



Anti-cancer Activity

All compounds were tested initially at a single high dose assay (10^{-5} M) in NCI60 cell panels and later selected for 5 dose assay.

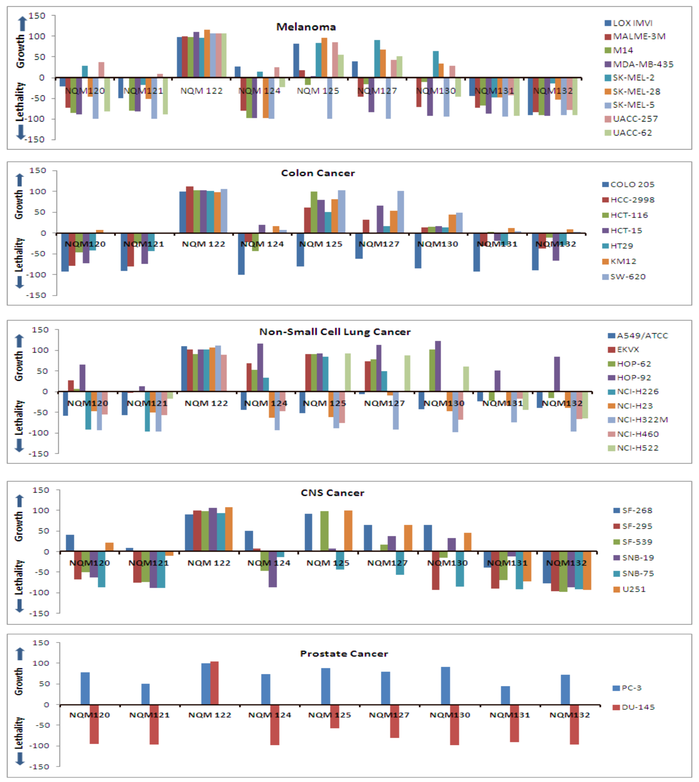


Figure 3: Single dose assay for new analogs.

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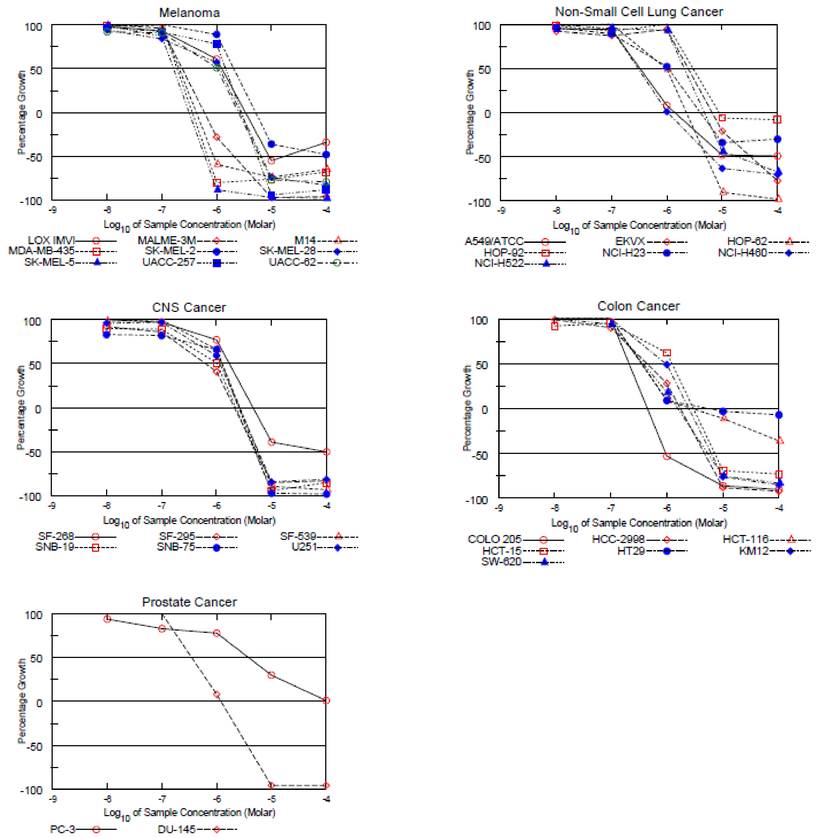

Figure 4: Five dose assay for NQM121.

Conclusion and Discussion

- A series of new anthraquinone analogs were synthesized and tested for their biological activities.
- These compounds have both anti-bacterial and anti-cancer properties.
- NQM 120 and NQM 121 are the most active analogs possessing electron donating group.
- Based on this primary study (Phase 1), more analogs (Phase 2) were synthesized. The anti-cancer test showed that these analogs are even more active against melanoma and CNS cancer.

References

1.Jones,K. E.; Patel, N.G.; Levy, M.A.; Storygard, A.; Balk, D.; Gittleman, J.L.; Daszak, P. *Nature* **2008**, 451, 990-993.

2.”Emergence of infectious diseases in the 21st century” Http://www.gideononline.com/2008/03/05/emergence-of-infecious-diseases-in-the-21st-century

Acknowledgements

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