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NOTE

Study of Sequential Cytotoxicity using 2,6-Diphenyl Piperidin-4-One Scaffold

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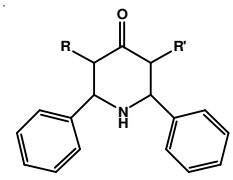
Novel compounds were synthesized in order to evaluate the theory of sequential cytotoxicity, which seeks to exploit the view that various cancer cells are particularly susceptible to successive attacks by cytotoxic agents. The series of analogous which lacking of olefinic bond and one olefinic bond were synthesized, which will predicted to be less cytotoxic than the compounds having two or three olefinic bonds. All the synthesized compounds have been screened for cytotoxic property by SRB-assay method against leukemic and colon cancer cell lines at four different concentrations. The results revealed that the predictions made regarding the viability of the theory were fulfilled. In addition, the significant properties of compound **5** and **6** towards cancerous cell lines, confirms their usefulness in serving as lead molecules for further development.

Key Words: 4-Piperidones, Cytotoxic agents, α,β-Unsaturated ketones.

The major emphasis in the present investigation is to design of compound as candidate for cytotoxic in order to examine a theory of sequential cytotoxicity. A number of years ago, the cytotoxicity of *E*-2-benzylidene cyclohexanone towards an epidermoid carcinoma of the nasopharynx (KB screen) was described in which this enone had an ED50 of 1.34 mM[1]. It was also proved that the number of α,β-unsaturated ketones display cytotoxic and anticancer properties[2-4]. Such molecules having ability to exclusively bind with thiol instead of amino or hydroxyl group of nucleic acid. Hence these compounds may be free from the problems of mutagenicity and carcinogenicity[5-7].

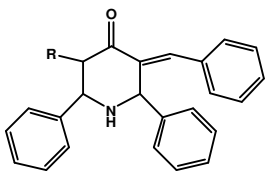
The theory of sequential cytotoxicity proposed by Dimmock *et al.*[8] that the successive release of two or more cytotoxic agents causes greater toxicity to malignant tissue than to normal cells. Thus alkylation with cellular thiol such as glutathione (GSH) may occur with the chalcone leading to the adduct-A. This reactive adduct-A forms adduct-B by reacting with another thiol molecules[9]. Hence two unsaturated keto chalcone is more active towards thiols than single unsaturated keto chalcone.

The compounds of **1**, **2** and **3** were prepared according to the literature procedure[10] by condensing 1 mol of ketone, 2 mol of benzaldehyde amd 1 mol of ammonium acetate. Compounds **4** and **5** were prepared as per literature procedure[11] by taking 1:1 ratio of 2,6 diphenyl pipridin-4-one and benzaldehyde for **4** and 1:2 ratio of 2,6 diphenyl pipridin-4-one and benzaldehyde for **5**. Compound **6** was prepared by acrylolylation of compound **5** with acrylolyl chloride[12]. The evidence from TLC and ^{1}H NMR spectroscopy and mass revealed that all compounds were isometrically pure.



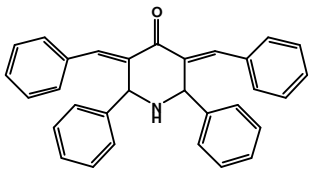
R = -CH$_3$,-CH(CH$_3$)$_2$
R' = -H, -CH$_3$

1,2,3

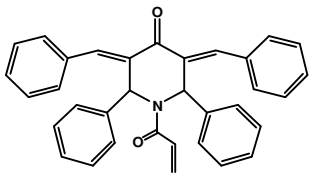


R = isopropyl

4



5



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All compounds were evaluated for cytotoxicity towards leukemic and colon cancer cell lines like Molt-4, K-562, HCT-15 and COLO-205 by SRB assay method[13]. Doxorubicin was used as standard. The cytotoxic results are expressed as GI_{50}.

TABLE-1
COMPOUNDS AND CYTOTOXIC DATA

Name of compound	m.p. (ºC), Yield (%)	Cytotoxic evaluation GI50 (μM)			
		K-562	Molt-4	HCT-15	COLO-205
1) 3-Methyl-2,6-diphenyl piperidin-4-one	88 (85)	>200	>200	>200	>200
2) 3-Isopropyl-2,6-diphenyl piperidin-4-one	127 (88)	>200	>200	>200	>200
3) 3,5 Dimethyl-2,6-diphenyl piperidin-4-one	131 (90)	>200	>200	>200	>200
4) 3-Phenyl methylidene, 5-isopropyl-2,6-diphenyl piperidin-4-one	250 (67)	>100	98.5	>100	>100
5) 3,5-*bis*(phenyl methylidene)-2,6-diphenyl piperidin-4-one	167 (27)	<0.1	59.5	>100	>100
6) 3,5-*bis*(phenyl methylidene)-1-acrylolyl-2,6-diphenyl piperidin-4-one	158-160 (50)	<0.1	39.5	64.1	30.4
7) Doxorubicin (standard)	-	<0.1	<0.1	<0.1	<0.1

Note: a) GI-50 value is Concentration of drug causing 50 % inhibition of cell growth; b) GI-50 value bellow 10 μM is considered as active; c) Compound **1**, **2** and **3** did not showed anticancer property

The LC_{50} (Concentration of drug causing 50 % cell kill) and TGI (concentration of drug causing total inhibition of cell growth) of synthesized compounds were found to be above the 100 μ molar.

The theory of sequential cytotoxicity state that successive release of two or more cytotoxic compounds may cause greater damage to tumor. The cytotoxic results indicate that the analogous **1**, **2** and **3** donot have anticancer properties. The analogue **4** having very less cytotoxicity than the analogous **5**. This is because of analogous **5** having two sites for thiolation whereas analogous **4** having only one site. Comparisons of **5** analog with **6** indicate that *N*-substitution increases the cytotoxicity. The cytotoxic data indicates that leukemic cell lines were most sensitive to these compounds in contrast to colon cell line which were more refractory (Table-1).

The values generated in the result indicate that the analogous **5** and **6** were more potent than the analogous **1, 2, 3** and **4**. *N*-acrylolylation of the secondary amino group gives compounds **6**, showed significant increased cytotoxicity. This result is in accordance with the theory of sequential cytotoxicity. These molecules may therefore be considered prototypic molecules for further development as candidate cytotoxic and anticancer agents.

REFERENCES

1. J.R. Dimmock, N.W. Hamon, K.W. Hindmarsh, A.P. Sellar, W.A. Turner, G.H. Rank and A.J. Robertson, *J. Pharm. Sci*., **65**, 538 (1976).
2. R.L. Jadhav and C.S. Magdum, *J. Pharm. Res.*, **9**, 3093 (2011).
3. J.R. Dimmock, D.W. Elias, M.A. Beazely and N.M. Kandepu, *Curr. Med. Chem.*, **6**, 1125 (1999).
4. J.R. Dimmock, N.M. Kandepu, A.J. Nazarali, T.P. Kowalchuk, N. Motaganahalli, J.W. Quail, P.A. Mykytiuk, G.F. Audette, L. Prasad, P. Perjesi, T.M. Allen, C.L. Santos, J. Szydlowski, E. De Clercq and J. Balzarini, *J. Med. Chem.*, **42**, 1358 (1999).
5. J.R. Dimmock, P. Kumar, A.J. Nazarali, N.L. Motaganahalli, T.P. Kowalchuk, M.A. Beazely, J.W. Quail, E.O. Oloo, T.M. Allen, J. Szydlowski, E. DeClercq and J. Balzarini, *Eur. J. Med. Chem.*, **35**, 967 (2000).
6. R.B. Silverman, The Organic Chemistry of Drug Design and Drug Action, Academic Press, Inc, San Diego, pp. 220-222 (1992).
7. J.A. Benvenuto, T.A. Connor, D.K. Monteith, J.W. Laidlaw, S.C. Adum, T.S. Matney and J.C. Theiss, *J. Pharm. Sci.*, **82**, 988 (1993).
8. J.R. Dimmock, M.P. Padmanilayam, R.N. Puthucode, A.J. Nazarali, N.L. Motaganahalli, G.A. Zello, J.W. Quail, E.O. Oloo, H.B. Kraatz, J.S. Prisciak, T.M. Allen, C.L. Santos, J. Balzarini, E. DeClercq and E.K. Manavathu, *J. Med. Chem.*, **44**, 586 (2001).
9. J.R. Dimmock, H.No. Pati, U. Das, J.W. Quail, M. Kawase and H. Sakagami, *Eur. J. Med. Chem.*, **43**, 1 (2008).
10. a) C.R. Noller and V.J. Ballah, *Am. Chem. Soci.*, **70**, 1853 (1948); b) S. Balasubramanium, C. Ramalingan and S. Kabilan, *Ind. J. Chem.*, **41 B**, 2402 (2002); c) T. Ravindran and R. Jeyaraman, *J. Org. Chem.*, **56**, 4833 (1991).
11. B.S. Furniss, A.J. Hannaford, P.W.G. Smithm and A.R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, Pearson Education, Inc., edn. 5, pp. 1032-1034 (2007).
12. Das Umashankar, J. Alcorn, A. Shrivastav, J.R. Dimmock, R.K. Sharma, E. De Clercq and J. Balzarini, *Eur. J. Med. Chem.*, **42**, 71 (2007).
13. P. Skehn, R. Storeng, A. Scudiero, J. Monks, D. McMohan, D. Vistica, T.W. Jonathan, H. Bokesch, S. Kenney, M.R. Boyd, *J. Nat. Cancer Inst.*, **82**, 1107 (1990).