Efficient biological activity of acridine synthesised by using efficient nano catalyst

Sujatha G.[1], Mathunika Devi A.[1], Lesy Josephine J.[2,3], Punitha P.[4] and Ramanathan P.[1*]
1. PG & Research Department of Chemistry, Thanthai Hans Roever College (Autonomous), (Affiliated to Bharathidasan University), Perambalur - 621220, Tamil Nadu, INDIA
2. Department of Chemistry, Government Arts College, (Affiliated to Bharathidasan University), ThuvakudiMalai, Tiruchirappalli – 620 022, Tamil Nadu, INDIA
3. Department of Chemistry, Immaculate College for Women, (Affiliated to Annamalai University), Manjakuppam, Cuddalore – 607 001, Tamil Nadu, INDIA
4. Department of Chemistry, Srinivasa Subbaraya Government Polytechnic College, Puttur, Mayiladuthurai (Dt), Tamil Nadu, INDIA
*ramanathanp2010@gmail.com

Abstract

A simple and efficient protocol for 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexa hydroacridine-1,8(2H,5H)-dione (MPTH) was synthesised by conventional method by using efficient nano catalyst. The crystallite sizes (L) and surface area (S) of TiO_2 are 10.44 nm and 140.32 m^2/g. MPTH displayed wide inhibitions on the KB cell appearance with IC_{50} values 25.06 µg. The IC_{50} values of the MPTH imply that methoxy substituted compound holds more inhibitory effect against the cancer cells.

Keywords: MPTH, TiO_2, NMR, XRD, SEM, Anticancer.

Introduction

Multicomponent reactants react in a solo event successively to form a novel product. MCRs get together the requirements of an environmentally responsive process, with fewer synthetic steps, less energy consumption and less waste production[10,15]. Acridine-1,8-diones are cytotoxic[1] and block potassium channels[6]. Acridinediones are synthesized in aqueous media[11-13]. Many methods have drawbacks such as use of dangerous organic solvents, extensive reaction times, low yields, development of elevation products and multistep synthesis. TiO_2 efficiently catalyzed synthesis of 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydr oacridine-1,8(2H,5H)-dione at 70 °C. Nanocrystalline rutile phase of TiO_2 was synthesised by the sol–gel method and analysed by X-ray diffraction and high resolution scanning electron microscopy.

Material and Methods

Materials and measurements: Dimedone, methoxybenzaldehyde and ammonium acetate were provided by Sigma-aldrich (St. Louis, USA). ^{1}H NMR (400 MHz) and ^{13}C NMR (400 MHz) spectra were recorded on Brucker spectrometer using DMSO solvent. XRD patterns were recorded using X–ray Rigaku diffractometer with Cu K_α source (30 kV, 100 mA), at a scan speed of 3.0000 deg/min, step width of 0.1000 deg, in a 2θ range of 20-80°.

Synthesis of 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione: 5,5-dimethylcyclohexane-1,3-dione (0.002 mm) reacts with ammonium acetate (0.001 mm) and methoxybenzaldehyde (0.1 mL) in ethanol medium with pinch of efficient nano catalyst at a suitable time (Table 1). The growth of the result was monitored on TLC (Scheme 1). The reaction was quenched in cold water. Product was filtered and then dried.

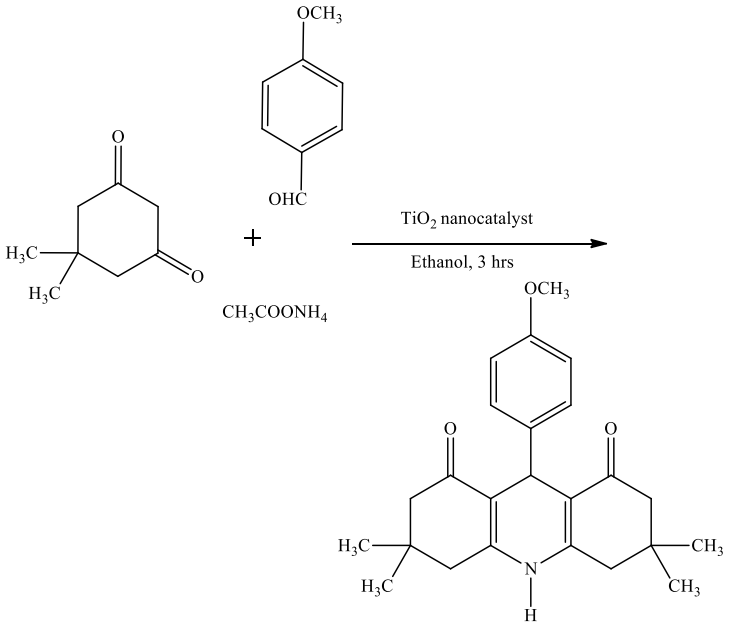
9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione: Anal. calcd. for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.94; H, 7.69; N, 3.68. ^{1}H and ^{13}C NMR (400 MHz, DMSO): δ 0.86 (s, 6H), 1.00 (s, 6H), 1.97 (d, J= 10.0 Hz, 2H), 2.16 (d, J= 12.2 Hz, 2H), 2.28-2.52 (m, 2H), 2.51 (d, J= 10.2 Hz, 2H), 3.88 (s, 3H), 4.74 (s, 1H), 6.69 (d, J= 8.8 Hz, 2H), 7.03 (d. J= 8.9 Hz, 2H), 9.27 (s, 1H) (Figure 1a); 5.20, 26.92, 29.57, 32.30, 32.59, 50.72, 63.17, 112.17, 113.84, 128.96, 139.82, 149.57, 156.84, 194.96 (Figure 1b). MS: m/z. 379.49 [M+].

Sol- gel synthesised TiO_2: The TiO_2 nanocrystal was arranged by sol-gel hydrolysis of titanium (IV) isopropoxide followed by calcination. About 1ml of titanium isopropoxide ($C_{12}H_{28}O_4Ti$) was soluble in 20ml isopropyl alcohol and the solution was dropped into 10ml of distilled water, pH 2-6 was adjusted by 1M HNO_3 for acidic condition and 1M NaOH for basic condition. The former colorless sol-gel of hydrous oxide was stirred strongly for 2 hrs and then kept overnight. The resultant substance was dried and calcinated at 600 °C for 2 hrs.

MTT assay: The cytotoxic movement of the compound was resolved utilizing MTT measure. $1x10^4$ cells for every cell were seen in 100 mL DMEM (Dulbecco's Modified Eagle Medium), add 10% FBS (Fetal Bovine Serum) in every well of 96-well micro culture plates and brood at 37ºC for 24 h in a CO_2 hatchery.

Table 1
Melting point, yield and time of reaction

Compound	MP (°C)	Yield (%)	Time (hrs)	Catalyst
MPTH	302	75	7	-
MPTH	303	94	3	TiO_2



Scheme 1: Synthetic route of 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

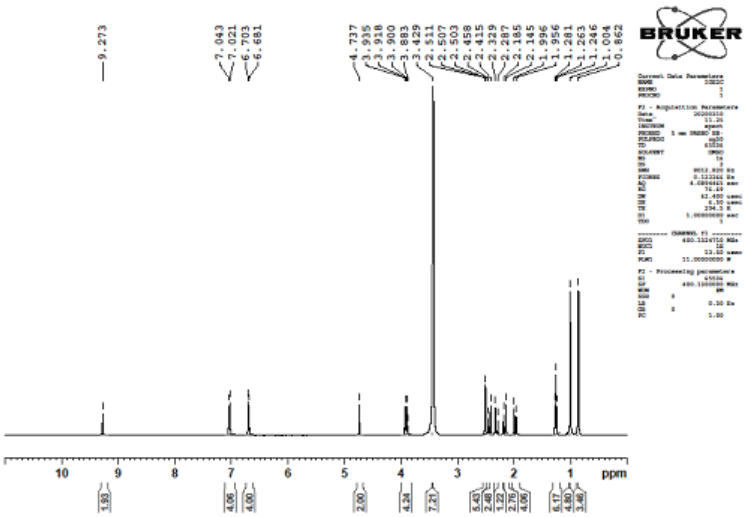


Figure 1a: ^{1}H NMR spectrum of 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

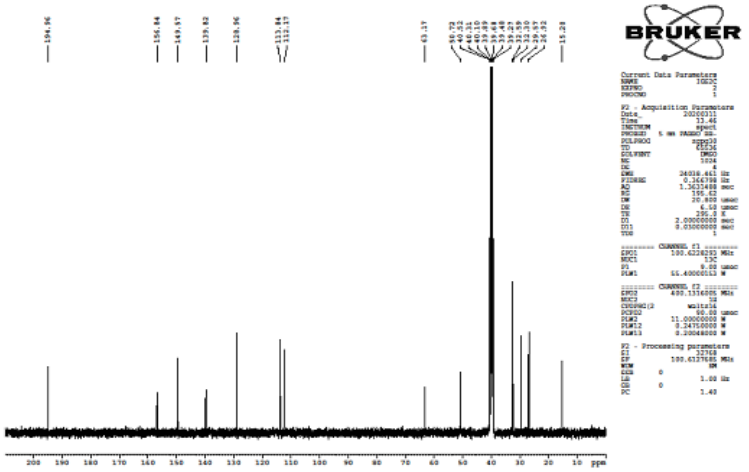


Figure 1b: ^{13}C NMR spectrum of 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

Subsequent to 48 h of hatching, 10 mL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazoliumbromide (5 $mgmL^{-1}$) was supplemented to every cell and the plates were additionally brooded for 4 h. At that point, the supernatant from every well was painstakingly evacuated, formazan gems were broken down in 100 mL DMSO and the absorbance was recorded at 570 nm wavelength.

Results and Discussion

XRD and SEM: XRD pattern of TiO_2 nanoparticle obtained by sol-gel method (Figure 2). The diffraction patterns of TiO_2 match with JCPDS pattern, body centered tetragonal with crystal constants a = b =3.7774A° and c = 9.501 A°. The crystallite size (L) of TiO_2 is 10.44 nm. The specific surface area of the nanocrystal has been deduced by employing the association S = 6/ρD, where S is specific surface area and ρ is material density. The designed surface area for TiO_2 is 140.32 m^2/g. The SEM of TiO_2 nanocrystal was displayed in figure 3. The measured crystallite size agrees with that obtained by XRD.

Cytotoxicity: The manufactured compound was subjected to the *in vitro* anticancer consequence of spirooxindole in KB cancer cell line. Spirooxindole action considerably reduced the percentage of cell feasibility in KB cancer cells. This recommended that spirooxindole management has tendency to restrain the enlargement of cancer cells through incubation. The reaction of cytotoxicity of compound MPTH with their applications is given in figure 4a and 4b.

These outcomes executed MTT test in KB cancer cells treated with similar concentrations of compounds for upto 24h. The results of the compound MPTH display wide inhibitions on the KB cell appearance with IC_{50} values of 25.06 µg. The IC_{50} values of the MPTH imply that methoxy substituted compound holds more inhibitory effect against the cancer cells.

Conclusion

A novel 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (MPTH) was synthesized by conventional method by using efficient nanocatalyst characterised by XRD and SEM. The compound was analyzed by NMR, mass spectral and biological activity like anticancer. MPTH analyzed anticancer activity by human blood cell (HRBC) membrane stabilization method.

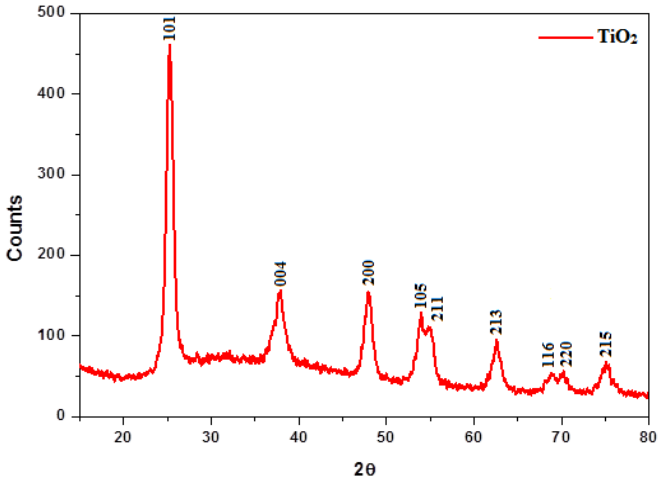


Figure 2: Powder XRD pattern of TiO_2 nanoparticles

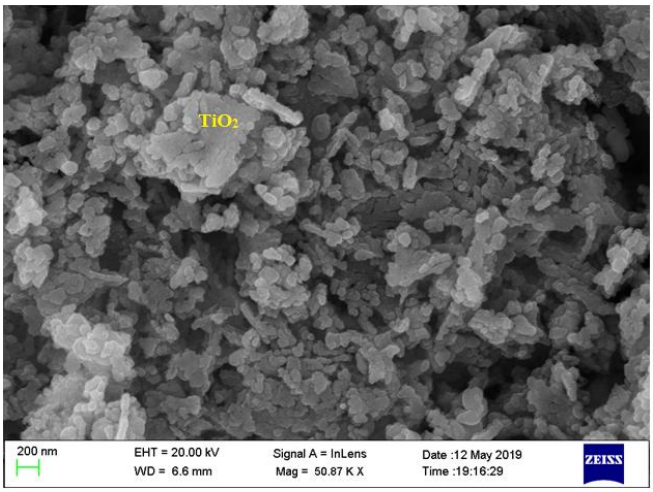


Figure 3: SEM image of TiO_2 nanoparticles

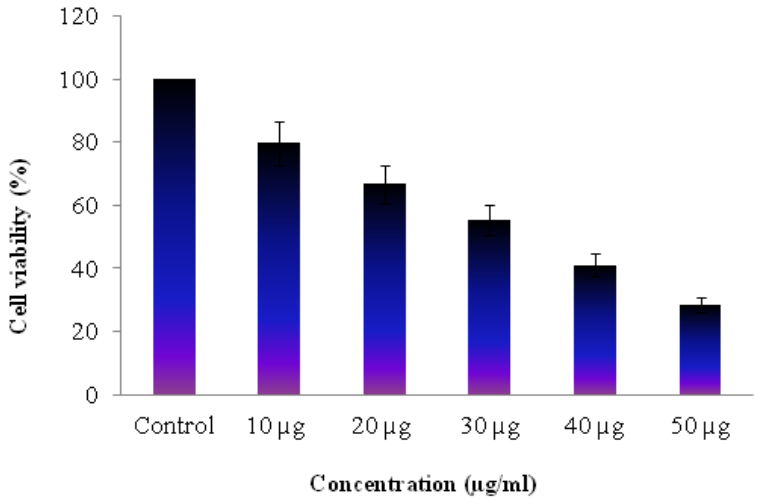


Figure 4a: Cell viability of compound MPTH

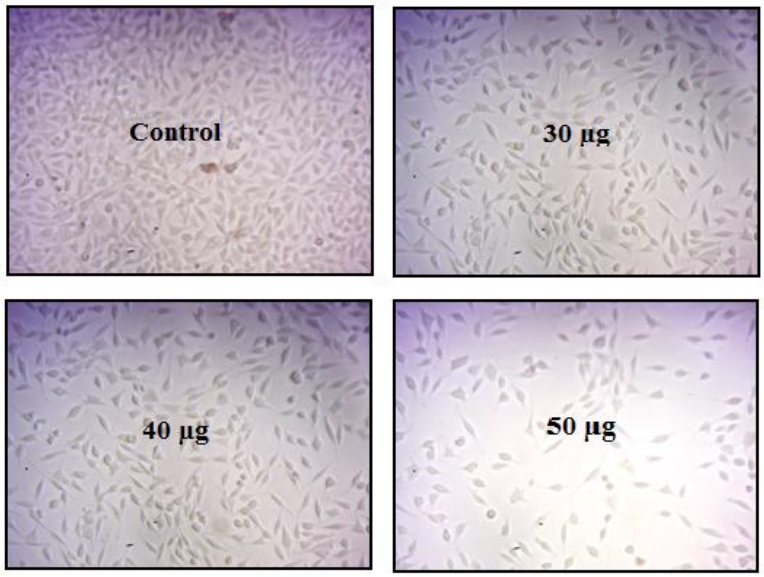


Figure 4b: Cytotoxicity images of compound MPTH at different concentrations

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References

1. Antonini I., Polucci P., Kelland L.R., Menta E., Pescalli N. and Martelli S., 2,3-Dihydro-1*H*,7*H*-pyrimido[5,6,1-*de*]acridine-1,3,7-trione Derivatives, a Class of Cytotoxic Agents Active on Multidrug-Resistant Cell Lines: Synthesis, Biological Evaluation and Structure−Activity Relationships, *Journal of Medicinal Chemistry*, **42**, 2535 **(1999)**

2. Aswin K., Logaiya K., Sudhan S.P.N. and Mansoor S.S., An efficient one-pot synthesis of 1,4-dihydropyridine derivatives through Hantzsch reaction catalysed by melamine trisulfonic acid, *Journal of Taibah University for Science*, **6**, 1 **(2012)**

3. Carole D.G., Michel D.M., Julien C., Florence D., Anna N., Séverine J., Gérard D., Pierre T.D. and Jean-Pierre G., Synthesis and antileishmanial activities of 4, 5-di-substituted acridines as compared to their 4-mono-substituted homologues, *Bioorganic & Medicinal Chemistry*, **13**, 5560 **(2005)**

4. Gamega S.A., Spicer J.A., Atwell G.J., Finlay G.J., Baguley B.C. and Deny W.A., Structure− activity relationships for substituted bis (acridine-4-carboxamides): a new class of anticancer agents, *Journal of Medicinal Chemistry*, **42**, 2383 **(1999)**

5. Girault S., Grellier P., Berecibar A., Maes L., Mouray E., Lemiere P., Debreu M., Davioud-Charvet E. and Sergheraet C., Antimalarial, antitrypanosomal and antileishmanial activities and cytotoxicity of bis (9-amino-6-chloro-2-methoxyacridines): influence of the linker, *Journal of Medicinal Chemistry*, **43**, 2646 **(2000)**

6. Gunduz M.G., Dogan A.E., Simsek R., Erol K. and Safak C., Substituted 9-aryl-1, 8-acridinedione derivatives and their effects on potassium channels, *Medicinal Chemistry Research*, **18**, 317 **(2009)**

7. Heravi M.M., Bakhtiari K., Zadsirjan V., Bamoharram F.F. and Heravi O.M., Aqua mediated synthesis of substituted 2-amino-4H-

chromenes catalyzed by green and reusable Preyssler heteropolyacid, *Bioorganic & Medicinal Chemistry Letters*, **17**, 4262 **(2007)**

8. Mansoor S.S., Aswin K., Logaiya K. and Sudhan S.P.N., An efficient one-pot multi component synthesis of polyhydroquinoline derivatives through Hantzsch reaction catalysed by Gadolinium triflate, *Arabian Journal of Chemistry*, **10**, S546 **(2017)**

9. Mansoor S.S., Aswin K., Logaiya K., Sudhan S.P.N. and Malik S., Silica-supported perchloric acid ($HClO_4$–SiO_2): a mild, reusable and highly efficient heterogeneous catalyst for multicomponent synthesis of 1,4-dihydropyridines via unsymmetrical Hantzsch reaction, *Research on Chemical Intermediates*, **40**, 357 **(2014)**

10. Safari J., Zarnegar Z. and Heydarian M., Practical, ecofriendly and highly efficient synthesis of 2-amino-4H-chromenes using nanocrystalline MgO as a reusable heterogeneous catalyst in aqueous media, *Journal of Taibah University for Science*, **7**, 17 **(2013)**

11. Shen W., Wang L.M., Tian H., Tang J. and Yu J.J., Brønsted acidic imidazolium salts containing perfluoroalkyl tails catalyzed one-pot synthesis of 1,8-dioxo-decahydroacridines in water, *Journal of Fluorine Chemistry*, **130**, 522 **(2009)**

12. Shi D., Shi J. and Yao H., Clean synthesis of 9, 10-diarylacridine derivatives in aqueous media, *Chinese Journal of Organic Chemistry*, **29**, 239 **(2009)**

13. Xia J.J. and Zhang K.H., Synthesis of N-substituted Acridinediones and Polyhydroquinoline Derivatives in Refluxing Water, *Molecules*, **17**, 5339 **(2012)**

14. Yang P., Yang Q., Qian X., Tong L. and Li X., Isoquino [4, 5-bc] acridines: Design, synthesis and evaluation of DNA binding, anti-tumor and DNA photo-damaging ability, *Journal of Photochemistry and Photobiology B: Biology*, **B84**, 221 **(2006)**

15. Zhu J. and Bienayme H., Multicomponent Reactions, Wiley, Weinheim, **15**, 2624 **(2005)**.

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