Indian Journal of Chemistry
Vol. 65, May 2026, pp. 439-444
DOI: 10.56042/ijc.v65i5.21545

A rare nitrene insertion followed by redox dimerization during the photolysis of 'azido-*meta*-meconine'

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Received 12 July 2025; accepted (revised) 15 May 2026

Aryl azides are 'green' reagents and provide a fascinating area of chemistry and have many uses in industry as pharmaceutical agents. Azidothymidine (AZT) is used to treat HIV-AIDS and a 2-dimethylaminoethyl azide (DMAZ) is a powerful explosive. The 'click' reaction based on these has been awarded the coveted Nobel Prize in 2022. 'Click' reaction is a 'green' regiospecific reaction since atom efficiency is very high as no atom loss occurs. Reactions of azides involve many unusual and fascinating transition states and intermediates. In this paper, is discussed the photochemistry of 'Azido-*meta*-Meconine'. Photolysis at 5°C using wavelength of 254 nm for 6 h has been carried out. The reaction product is subjected to preparative Thin Layer Chromatography (TLC), two bands namely an 'Upper band' and a 'Lower band' have been separated, molecular weight values in LC-MS spectrum differs from each other by six atomic mass units (six hydrogens). One part of the reactive intermediate underwent addition of hydrogen (reduction) and other dehydrogenation (oxidation) which thus constitutes a rare example of dimerization of nitrene intermediate previously unknown in the literature. Detailed LC-MS studies have provided evidence for the formation of two products with yield around 94.99%, which is an unusually high yield for such photochemical reactions. Further, spectroscopic studies (UV-Visible, FT-IR, ^{1}H NMR, *etc*.) have also been carried out for corroborating the successful formation of these two products.

Keywords: Aryl azides, Photolysis, Nitrene insertion, Redox dimerization

Aryl Azides are considered 'Green' reagents as either on thermal or photochemical reactions a loss of Nitrogen molecule occurs, which is innocuous to the environment and does not cause any pollution[1]. Photochemical reactions of aryl azides involve formation of a myriad intermediate species[2,3]. These are 'transient species' which could be either 'short-lived' or 'long-lived' and are identifiable by different spectroscopic techniques, more particularly by Ultrafast Laser Spectroscopy[4]. Substituents play almost a 'mysterious' role in their reactions[5]. Thus, the ring expansion of nitrenes to azepines has been described as a 'most enigmatic reaction'. Among the many intermediates involved are singlet and triplet nitrenes, benzazirines, heterocumulenes. Even the formation of a cyclopentadiene nitrile has been documented **(SI-I)**[6].

In some cases, "Nitrene-Carbene" conversion (Crow-Wentrup pathway)[7] and ring extrusion reaction leading to the formation of a pyridine ring is known. Triplet nitrenes lead to the formation of amines and azo compounds and singlet-triplet conversion is temperature dependent, lower temperatures favoring the formation of the triplet products.

Computational chemistry of nitrenes has been an active field with seminal contributions from W. T. Borden[8]. The reaction of aryl azides with alkynes, without loss of nitrogen, leading to regiospecific formation of 1, 4-disubstituted-1, 2, 3-triazoles is now known as the 'click' reaction, which was recently decorated with the 2022 Nobel Prize. The earlier version of 1, 3-dipolar cycloaddition reactions were extensively investigated by Rolf Huisgen[9], but the reaction took many days to complete. In 2001, Sharpless accelerated the process by use of Cu (II) ions and a year earlier Meldal had also published on this reaction[10,11].

E. F. V. Scriven's book on Azides also highlights their industrial applications, Peter A. S Smith coined the phrase "Cycloperambulation" reactions [loc. cit.] **(SI-II)**. Hans Suschitzky also contributed significantly

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to the field. On aspects of photo-chemical fast spectroscopy M. S. Platz's group at the Ohio State University, Columbus, led the way. A question that arises is "Are these intermediates mere curiosities or do these play a role in understanding the origin of human diseases, *e.g*., "Cataractogenesis"[12].

We have successfully used aryl azides earlier for preparing photoresists for microlithography, the workhorses of the burgeoning multibillion-dollar microelectronics industry[13]. Aryl azides have been used by us in crosslinking Poly (3-hexylthiophene) (P3HT) with two novel biaryl-based bisazides for better device performance[14]. We have used aryl azides reagent successfully in a two-step synthetic strategy to prepare water-soluble nanocarbon materials (WSNCMs)[15-19]. These WSNCMs possess strong anti-cancer activity against different cancer cell lines *in vitro* with no cytotoxicity. We plan to use the above strategy on Graphene, which could lead to applications in the fabrication of nano devices and materials sciences.

We have previously published on "Viswamayene" formed *via* a concomitant ring expansion cum ring extrusion reaction involving not only azepine ring formation but also formation in the same reaction of a pyridine ring which further corroborates involvement of a nitrene-carbene conversion[20]. Ultrafast Infrared and UV–Vis spectroscopic studies on 2-methoxy-6-methoxycarbonylphenyl azide involve 'long-lived' transient species with a life span of 750 ps[21]. We have also used aryl azides as photo-crosslinkers for studying protein-protein interactions[22,23]. A mere short exposure to incident UV light brings about major crosslinking in proteins and the kinetic phenomenon does not damage the original protein which retains its biological activity.

Our study using azido dimethylsuccinylosuccinate showed the formation of a 'trimeric' pentacyclic product identified by different spectroscopic techniques

In this paper, photolysis of 'Azido-*meta*-Meconine' **(SI-III)** has been investigated by us and the study points towards the involvement of newer pathways. The compound '*meta*-meconine' has been investigated by very well-known chemists, Sir Robert Robinson and the alkaloid chemist R.H.F. Manske, who investigated the nitration, bromination and other such reactions of '*meta*-meconine' form a very classical study of this parent compound[24,25].

We have reported two products namely 'Upper band' (500 a.m.u) and 'lower band' (494 a.m.u), isolated using preparative Thin Layer Chromatography (TLC) upon photolysis of 'Azido-*meta*-Meconine'. LC-MS studies provided evidence for the formation of these two products with yield amounting to 94.99%. The reactive intermediate formed undergoes nitrene insertion into -CH- bond of acetonitrile followed by a rare redox dimerization (addition of hydrogen (reduction) on one part of the molecule and dehydrogenation (oxidation) on the other part) accompanied by ring expansion (Fig. 1). The formation of these products is most unusual and has not been reported in the literature before.

Results and Discussions

GC-MS studies on Photolysis of 'Azido-*meta*-Meconine'

Unexpected formation of the Acetonitrile adduct

'Azido-*meta*-Meconine' (FAB-MS, M^+, m/z 235) after photolysis at 254 nm and samples were taken out after every 10 min and injected into GC-MS inlet (200°C) showed a peak at m/z 207 attributed to the formation of the corresponding nitrene by loss of nitrogen from the azide **(SI-IV)**. Another peak was observed at m/z 248, which constituted a surprising result, this apparently arose by insertion of the nitrene into the solvent acetonitrile. Whose intensity increased with exposure time **(SI-V)**. Previously acetonitrile has been routinely used as a solvent in such photochemical reactions and never has any such adduct formation been observed. This is a very special and rather uncommon observation pointing towards an unusually 'long-lived' nitrene. This GC-MS study is to be considered as an initial study which led to us taking a more detailed study using LC-MS (**SI-VI**).

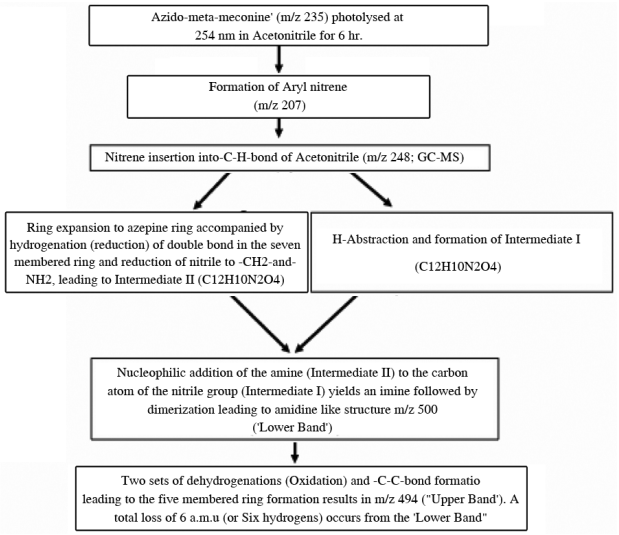

Fig. 1 — Flow chart shows the proposed steps involved in formation of "Upper Band" and "Lower Band" upon photolysis of "Azido *meta*-meconine" in acetonitrile (as solvent) at 5°C

LC-MS Studies on products from Photolysis of 'Azido-*meta*-Meconine'

LC-MS studies on (2Z)-2-(1,3-dihydro-5,6-dimethoxy-1-oxoisobenzofuran-7-ylimino)-N-(2-((6Z,8E)-3a,4-dihydro-6,7-dimethoxy-3-oxo-1*H*-furo[3,4 c]azepin-5(3*H*)-yl)ethyl)acetamidine

In the LC-MS spectrum of (2Z)-2-(1,3-dihydro-5,6-dimethoxy-1-oxoisobenzofuran-7-ylimino)-N-(2-((6Z,8E)-3a,4-dihydro-6,7-dimethoxy-3-oxo-1*H*-furo[3,4-c]azepin-5(3*H*)-yl)ethyl) acetamidine, RT = 6.99 min, a peak was observed at m/z 501.1 along with other fragment peaks. The structure based on mass fragmentation pattern is proposed here. MS fragments are observed at m/z 240.1 and 262, since the recording was done in positive ion mode these peaks are interpreted as m/z 239.1 and 261 respectively. The sum of these two peaks adds to give the molecular weight of this compound which is m/z 500.1. The proposed chemical structure consists of two units. The first unit of m/z 239.1 contains a dihydroazepine formed regio-specifically towards the carbonyl end. The formation of azepine skeleton occurs presumably through a complicated series of rearrangement reactions including ring expansion to possible heterocummelene.

The second unit of m/z 261 consists of an intact aromatic ring and the dehydrogenation in the adduct takes place. Both these units are linked to each other presumably by C-N bond *via* redox dimerization. Such a system would not be trivial in the analysis of its NMR studies. The mass spectrum of the parent compound clearly shows asymmetric fragmentation and not symmetric fragmentation. Both the fragments observed have odd values and thus contain an odd number of nitrogen atoms. The determined molecular formula and molecular weight for the complete unit are $C_{24}H_{28}N_4O_8$ and 500.5 a.m.u, respectively. The LC-MS spectrum and proposed structure of m/z 500.1 is shown below (Fig. 2 and Fig. 3). The proposed mechanism for formation of m/z 500.1 is shown in **(SI-VII to SI-IX).**

LC-MS studies on 5-[(3Z)-3-[(5,6-dimethoxy-3-oxo-1,3-dihydro-2-benzofuran- 4-yl)imino]-2-imino-3,4-dihydro-2*H*-pyrrol-4-yl]-6,7-dimethoxy-1*H*,3*H*,5*H*-furo[3,4-c]azepin-3-one

In the LC-MS spectrum of5-[(3Z)-3-[(5,6-dimethoxy-3-oxo-1,3-dihydro-2-benzofuran-4-yl)-imino]-2-imino-3,4-dihydro-2*H*-pyrrol-4-yl]-6,7-dimethoxy-1*H*,3*H*,5*H*-furo[3,4-c]azepin-3-one, RT = 6.71 min, a peak was observed at m/z 494.1 along with other fragment peaks.

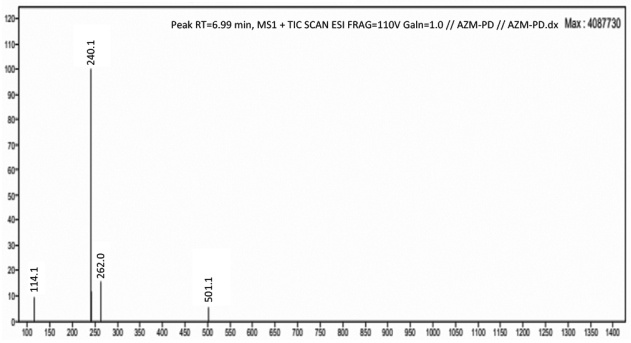

Fig. 2 — LC-MS of Photolyzed 'Azido-*meta*-meconine' at RT= 6.99 min

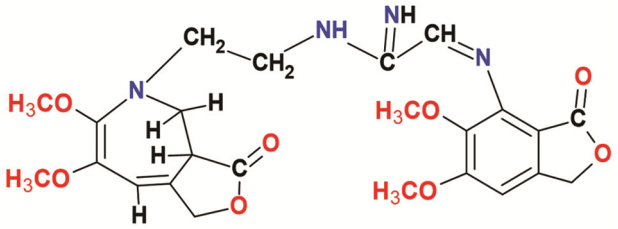

Fig. 3 — Proposed Structure of m/z 500.1

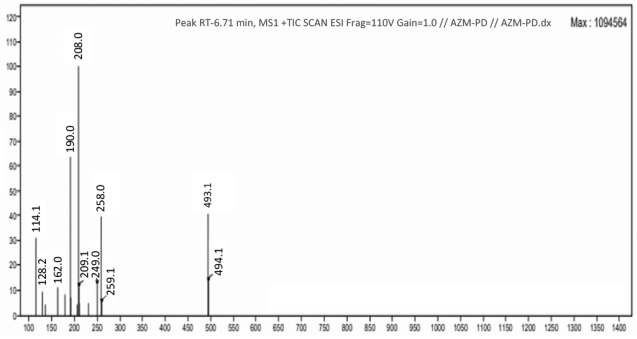

Fig. 4 — LC-MS of Photolyzed 'Azido-*meta*-meconine' at RT= 6.71 min

The determined molecular formula and molecular weight are $C_{24}H_{22}N_4O_8$ and 494.45 a.m.u. respectively. This differs from the parent compound with molecular weight of 500.1 by six atomic mass units (six hydrogens). The proposed mechanism for formation of m/z 494.1 is shown in **(SI-X)** (Fig. 4).

Thus, the two structures are related to each other and m/z 500.1 and 494.1 constitute 53.66 and 41.33% which is 94.99% of the total product **(SI-XI)** (Fig. 5). This is an unusually high yield considering that most azides yield in reaction of azides are often calculated based on azide converted which can be in the range around 28-30%. Our observed yield of 95% far exceeds the yield observed in photolysis of other aryl

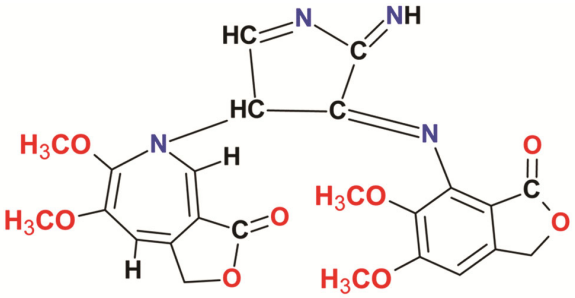

Fig. 5 — Proposed Structure of m/z 494.1

azides, this observation of our constitutes an unusual observation.

It needs to be reiterated that in m/z 500 no symmetric fragmentation was observed and hence no peak at m/z 250 was observed and the fragmentation occurred asymmetrically. This piece of information was very crucial in elucidating the structure of the new compounds. Both these molecules are tertraza-containing structures and are very attractive as metal-capturing agents. It is suggested that, both the above compounds can exhibit allylic shifts of hydrogen with concomitant shift of double bonds, and tautomer with different percentages are possible. We plan to carry out conformational studies using modern software which will bring to light the conformation possibilities of these compounds involving ring inversion, nitrogen lone pair inversion and ring flipping into crown, boat like conformations[26]. Such a study may open up possibilities for deeper study into the transition states and intermediates involved in the reaction pathways[27]. These compounds are new and not described in the literature before and could find possible uses in the different areas of sciences.

UV-Visible studies

The UV-visible spectrum of both isolated products (Lower Band and Upper band) was recorded in methanol and showed strong peaks at 249, 271, 298, and 340 nm (Fig. 6). A very broad strong absorption is observed in the range of 270- 340 nm which is indicative of highly extended conjugation system.

This makes it very different from the UV-visible spectrum of 'Azido-*meta*-Meconine' **(SI- XII)**. This demonstrates successful formation of both products.

FT-IR Spectral Studies

FT-IR spectrum of both isolated products (Lower Band and Upper band) was recorded in methanolic solution and is shown in (Fig. 7). The peak at 3318 cm^{-1} is attributed to (-N-H stretching), 2943 cm^{-1}

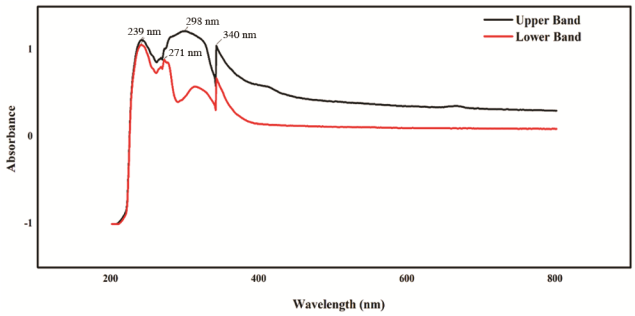

Fig. 6 — UV-Visible spectrum of 500.1m/z (Lower Band) and 494.1 m/z (Upper Band)

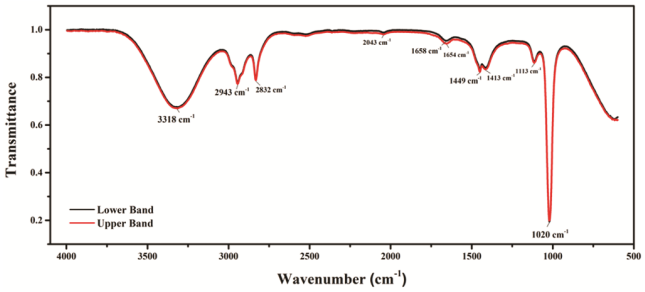

Fig. 7 — FT-IR spectrum of 500.1m/z (Lower Band) and 494.1 m/z (Upper Band)

attributed to (-CH_3 stretching), 2832 cm^{-1} to (-CH_2 stretching), strong peak at 1020 cm^{-1} is attributed to (-CH- stretching). No azide peak was observed in the spectra and thus indicates again successful formation of both products upon photolysis and also explains their high yields.

NMR Spectral Studies

^{1}H NMR spectrum of Upper band

^{1}H NMR spectrum of Upper band was measured in deuterated methanol using SA-Varian 500 MHz NMR. Signals were obtained at δ 2.71 (s) ppm attributed to C*H* of the five membered ring system. The δ 3.56 (m) and 3.62 (s) ppm are attributed to -OCH_3 of azepine and δ 3.80 (s) and 3.88 (s) ppm to aromatic ring system respectively. The δ 4.76 (s) and 5.13 (s) ppm are attributed to -CH_2 present in lactone ring of azepine and aromatic ring respectively. The proton at δ 6.38 (m) ppm is assigned to C*H* in azepine ring nearby CH_2 of the lactone. The proton at δ 6.82 (m) ppm is assigned to aromatic ring and the proton at δ 7.10 (s) ppm is attributed to -C*H* in azepine ring nearby carbonyl of corresponding lactone ring. Value at δ 7.35 ppm (m) is attributed to -C*H* on -C=N- in the five membered ring. (**SI-XIII, SI-XIV**).

^{1}H NMR spectrum of Lower band

^{1}H NMR spectrum of Lower band was measured in deuterated methanol using SA-Varian 500 MHz NMR. Signals were obtained at δ 2.32 (m) ppm and δ 2.56 (m) ppm are attributed to two CH_2 next to the nitrogen atom inside reduced azepine system. Peaks obtained at δ 2.71 (m) and 3.06 (m) ppm are attributed to two asymmetric -C*H* present in the reduced azepine system. Peak obtained at δ 3.21 (m) ppm is assigned to -C*H* present in the reduced azepine system nearby fused lactone ring. The peaks obtained at δ 3.50 (s) and 3.51 (s) ppm are attributed to -OCH_3 of reduced azepine ring and values at δ 3.80 (s), 3.88 (s) ppm are attributed to -OCH_3 of aromatic ring. Peak obtained at 5.38 (t) ppm is attributed to -CH_2 present in lactone ring fused with aromatic system and the peak obtained at 5.13 (s) ppm is attributed to -CH_2 present in lactone ring fused with reduced azepine ring. The peak obtained at δ 6.1 (m) ppm is attributed to the C*H* present nearby methoxy group in the reduced azepine ring. Peak obtained at δ 6.82 (s) ppm is attributed to the -C*H* present in the aromatic system. The peak obtained at δ 7.35 (m) ppm is attributed to the -C*H* present next to the nitrogen atom outside the aromatic system (**SI-XV, SI-XVI**).

Conclusions

Aryl Azides continue to interest chemists, biochemists, and the polymer and pharmaceutical industry. Many transition states, intermediates and pathways are known in the reaction of aryl azides. It may be pointed out that aryl azides are now considered 'green' reagents as their thermal and photochemical reaction involves an innocuous loss of nitrogen gas which does not lead to any pollution. Generally, photolysis of aryl azides yields is low in the range of 28-30%, accompanied by much tarry material which is difficult to characterize. Hence yields of products are reported based on azide converted and not the starting material. We report here the photolysis of an aryl azide, 'Azido-*meta*-meconine', with an usually high yield of 94.99% as determined by LC-MS study. Reported here is the formation of a nitrene insertion product into solvent acetonitrile, not reported earlier. On more careful investigation we unraveled the formation of two major products which differ from each other by six hydrogen atoms.

The first product has molecular weight of m/z 500.1 and its mass fragmentation shows that it splits asymmetrically into fragments of mass 239.1 and 261 a.m.u. which adds to the molecular weight of 500.1 a.m.u. This is a tetra-aza compound with an unusual formation of dihydroazepine and azepine in the same reaction product, along with nitrene insertion into solvent acetonitrile, accompanied by redox dimerization. The other compound has molecular weight of m/z 494.1 and differs from the parent compound only in six hydrogen atoms.

Thus, special feature we have reported in this paper is nitrene insertion into -CH- bond of acetonitrile followed by a very rare redox dimerization involving ring expansion accompanied by reduction. The formation of these products is most unusual and has not been reported in the literature before and these structures could possess interesting chemical and biological activity.

Experimental Section

All the reagents and solvents were purchased from Sigma Aldrich (greater than 99.9% purity). Agilent 5973D US7 GC/ MS instrument was used in GC/ MS experiments at the Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210, United States. FT-IR studies were performed using 2 (Perkin Elmer), ^{1}H NMR Spectra was recorded using Varian 500MHz in deuterated methanol, and UV-Visible Spectra was recorded using UV-VIS Spectrophotometer (Number: 29-1950-01-0170) with Spectral Bandwidth of 2.00 nm. LC-MS Spectrum of the compounds was recorded using the LC system - Agilent 1260 infinity II and MS system – LC/MSD IQ.

GC-MS Experiment

'Azido-*meta*-meconine' was photolysed at 254 nm in a dilute solution of acetonitrile and subjected to GC-MS analysis every 10 min over 3-4 hr.

Photolysis of 'Azido-*meta* Meconine' at 5°C 25 mg of 'Azido-*meta*-Meconine' was taken and dissolved in 50 mL acetonitrile. Photolysis was carried out at 254 nm using 6W UV-Lamp for 6 hr at 5°C **(SI-XVII)**. The reaction mixture was subjected to slow evaporation and 20 mg (yield) was obtained **(SI-XVIII)**.

Preparative Thin Layer Chromatography (TLC) studies

From the Photolyzed product, two products having molecular weights 500.1 a.m.u and 494.1 a.m.u respectively (confirmed from LC-MS studies) were isolated using Preparative TLC. The eluting solvent

system consisted mixture of Dichloromethane (DCM) and Ethyl acetate (EA) in a ratio of 7.5:1. The Photolyzed product was dissolved in Ethyl acetate **(SI-XIX)**.

Supplementary Information

Supplementary information is available in the website https://nopr.niscpr.res.in/handle/123456789/58776.

Data availability

All data that supports this study is available in the article and supplementary material.

Declaration of Funding

This research did not receive any specific funding.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

Authors thank Prof. Matthew S. Platz, (for GC-MS), formerly at Ohio State University, Columbus, OH, USA and presently at University of Hawaii, USA; Dr. Christopher Hadad, (For the suggested reaction pathway), Professor, Department of Chemistry and Biochemistry, The Ohio State University; Dr. Neel Sarovar Bhavesh (NMR), ICGEB, New Delhi; Dr. Sripadi R. Prabhakar (For MS), CSIR-IICT, Hyderabad. This work was made possible under a faculty exchange programme (SVE) between St. Stephen's College, Delhi, India and Brown University, Providence, RI, USA.

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