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Subscription: $35 per year to members, $100 per year to non-members. Single copy: $50.
The Chemist (ISSN-0009-3025) is published online by The American Institute of Chemists, Inc.
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ANNOUNCEMENTS

Invitation to Authors
We live in a time in history when one of the major drivers of economic growth, employment and quality of life is science and its technological applications. Examples include self-driving cars, which are being road tested and are projected to provide safer highway driving conditions in the near future, and 3-D printers, which are printing human prostheses and are projected to print live parts for organ transplant. In this context, one of the fastest-growing areas with a very high degree of career growth is mechatronics, a hybrid of various fields such as mechanical engineering, electronics, telecommunication engineering, information systems, computer science, biological systems and nanotechnology. Research and development in nanoscale chemical and physical sciences still provide the foundational know-how for mechatronics. As Professor Mirkin stated in his 2016 AIC Gold Medal Speech, “Nanoscience and technology hold promise to transform diverse fields spanning medicine, information technology, electronics, materials science, chemistry, energy, and the environment” (p.1). Siji Mathew and co-authors have investigated the efficiency of dye-sensitized solar cells developed using black plum, grapes skin, mangosteen, raspberry and beetroot as natural sensitizers. Amrutha P. Thankachan and co-authors reported a mild reaction protocol for C-S cross-coupling reactions of aryl and alkyl thiols with aryl halides catalyzed by zinc. Alexandra Knopp and co-authors compared the diagnostic and predictive values of tumor markers CYFRA 21-1, NSE, and CEA for the serodiagnosis of lung cancer. In the Public Understanding of Chemistry section, Todd A. Houston explored the Chemistry-Music connection by tuning in on transition metals by revisiting Newlands’ law of octaves. Finally, Mary van Muelken portrayed a veteran chemist, Dr. Lawrence Duffy—a navy veteran and long-time fellow of The AIC.

The Chemist Volume 88, Issue Number Two, 2016 marks the completion of five years since the journal was resurrected and relaunched as a refereed official online journal of The American Institute of Chemists. Also, the Public Understanding of Chemistry section completes five years. For reference, this issue contains a five year volume index. During this period, the line-up of articles spanned scientific chemical research to education and public understanding of chemistry. I would like to thank the members of the Editorial Review Board for their pro-bono support reviewing manuscripts and helping to maintain the quality of the journal. Besides experts in chemistry and science in general, each issue of the journal has received help from experts such as Dr. Penelope Fritzer from the field of English. The role of the editorial assistants cannot be underestimated either. The support of Dr. Valerie Bristor, Dean of the College of Education at Florida Atlantic University who may be considered a friend of chemistry in providing a home base for The Chemist for the past five years, is much appreciated and should not go unnoticed by my respected colleagues in chemistry. Often, it is humbling to realize that chemists need non-chemists in order to lift us up, to move forward, and to bring us out of our ivory towers so that we can connect with fellow humans, our neighbors for the sake of our own survival, and that of chemistry so that our field can continue to be a contributing factor in economic growth and employment, and in improving the quality of life on earth.
Nanoscience and technology hold promise to transform diverse fields spanning medicine, information technology, electronics, materials science, chemistry, energy, and the environment. Nanomaterials, in particular, are facilitating rapid and meaningful advances at the intersection of biology, chemistry, and medicine. This is due in part not only to their multi-functionality, but also their size, which is ideal for interacting with biological structures, both in vitro and in vivo. Spherical nucleic acids (SNAs), structures first reported by our group in 1996, are typically composed of spherical nanoparticles functionalized with a dense array of highly oriented oligonucleotides (e.g., DNA, RNA) (Figure 1).

They have emerged as important tools in the life sciences and biomedicine, enabling advances in the development of high sensitivity, point-of-care medical diagnostic tools (SNAs can serve as labels for assays that take place both outside and inside of living cells) and therapeutics (SNAs can act as potent gene regulation and immunotherapy agents). Indeed, SNAs, structures with no known natural equivalent, are unlocking the potential of nucleic acids in these fields due to their unique architecture-dependent chemical and physical properties. Furthermore, SNAs can be used as “programmable atom equivalents” (PAEs) to build designer crystalline materials, where the lattice symmetry and spacing can be tailored through choice of nanoparticle size and composition and nucleic acid length and sequence.

These nucleic acids function as programmable “bonds” between nanoparticle “atoms” and can be analogized to a nanoscale genetic code for directing particle assembly. The tunability of these nucleic acid bonds allows one to define a powerful set of design rules for synthesizing superlattices with more than 30 distinct lattice symmetries, in multiple well-defined crystal habits.

These SNA-based superlattice materials can dynamically respond to biomolecular stimuli, including other nucleic acids and enzymes, such that their structure, properties, and functions can be tailored on demand. This unique genetic approach to materials design yields nanoparticle architectures that can be used to catalyze chemical reactions, manipulate light-matter interactions, investigate energy transfer between nanostructures, and improve our fundamental understanding of crystallization processes.

Fig 1. Schematic of a spherical nucleic acid (SNA) with a gold nanoparticle core and a single-stranded DNA shell.
Investigation of the Efficiency of Dye-Sensitized Solar Cell Using Natural Dyes as Photo Sensitizer

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Abstract: Dye-sensitized solar cells (DSSCs) were constructed by using the black plum, grapes skin, beetroot, mangosteen, and raspberry as natural sensitizers of anatase-based nanostructure TiO\textsubscript{2} thin film coated on fluorine-doped tin oxide (FTO) conducting glass. \textit{N,N,N-tris-(2-methoxy-naphthalene-1-yl)-N,N,N-triphenylbenzene-1,3,5-triamine} [MNTT] was used as hole transporting material. The photovoltaic properties of the cell have been studied and the best overall solar energy conversion efficiency of 0.94\% was obtained under air mass (AM) 1.5 irradiation.

Key Words: natural photosensitizers; DSSCS; solid state electrolyte; photovoltaic; solar energy.

INTRODUCTION

Dye-sensitized solar cells (DSSCs) have attracted considerable attention due to their environmental friendliness and low cost of production. A DSSC is composed of a nanocrystalline porous semiconductor electrode-absorbed dye, a counter electrode, and a hole transporting material. In DSSCs, the dye as a sensitizer plays a key role in absorbing sunlight and transforming solar energy into electric energy. Numerous metal complexes and organic dyes have been synthesized and utilized as sensitizers. The DSSCs sensitized by Ru-containing compounds are reaching conversion efficiencies of 11-12\%, the highest efficiency reported by Chiba and Islam [1]. However, ruthenium dyes are not suitable for environmentally friendly photovoltaic systems. Ruthenium is expensive and environmentally hazardous. Ruthenium compounds are treated as highly toxic and carcinogenic. When ruthenium compounds are heated in the presence of air, they form ruthenium tetroxide, which is a highly volatile and toxic compound that damages the eyes and upper respiratory system [2]. On the other hand, natural dyes, such as pigments used in food colouring, are easily and safely extracted from plants [3]. It means that they do not require complex synthesis or toxicity test [4] and can be used in DSSCs. Since natural dyes have low cost of synthesis and are environmentally friendly, they are considered as a viable option for dye-sensitized solar cells in future research [5].

Roy et al. indicated that when using Rose Bengal dye as sensitizer, the \textit{J}\textsubscript{sc} and \textit{V}\textsubscript{oc} of their DSSC reached 3.22mA.cm\textsuperscript{−2} and 0.89 V, respectively, resulting in a 2.09\% conversion efficiency [6]. Furthermore, Wang et al. carried out structural modification of coumarin and used the coumarin derivation dye as sensitizer in their DSSC, which provided an efficiency of 7.6\% [7]. For ideal performance and excellent efficiency, the electrolyte should have high ionic conductivity so that it can transfer oxidized/reduced species to respective electrodes efficiently and should prevent back electrode reactions completely. Polyethylene oxide (PEO) has some exceptional properties of good mechanical strength, film forming properties, and excellent ability to form complexes with the ionic salts. Polymeric electrolyte is an ideal choice used in lithium ion batteries, super capacitors, photoelectrochromic display devices, and solar cells [8].

Organic liquid electrolytes dye-sensitized solar cell (DSSC) has attractive features of high energy conversion efficiency and low production cost [9, 10]. However, in the presence of traditional organic liquid electrolytes in such cells have some problems, such as lower long-term stability and a need for airtight sealing. One of the major
problems of such DSSC is the electrolyte loss caused by the leakage and volatility of the electrolyte solution that lowers the durability of the cell. Solid state dye-sensitized solar cells [DSSC] are promising due to their large potential to convert solar energy to electrical energy at low cost and their capability to solve the leakage or sealing problems that exist in liquid electrolyte dye-sensitized solar cells [11].

Natural dyes can replace synthetic dyes since they can be easily extracted from fruits, vegetables, and flowers with simple and direct chemical procedures, whereas the earlier fabrication process normally requires many steps, procedures, organic solvents, and purification procedures. In the present investigation, five natural dyes were extracted from black plum, grapes skin, beetroot, mangosteen, and raspberry. Beetroot (Beta vulgaris) is the main source of natural red dye, known as “beetroot red”. Betanin is the main colouring compound present in red beetroot juice. Betanins are aromatic indole derivatives and have the requisite functional groups (-COOH) to bind better to the TiO$_2$ nanostructure [12]. Grape skin extract is a purplish-red liquid with a fruity odor. Anthocyanins are mainly responsible for the red colour of grapes due to the highly-coloured flavylium cation [13]. Black Plum is a purple-coloured, oval-shaped tropical berry with a unique taste, flavor, and colour. Syzygium species are reported to be very rich in tannins, flavonoids, essential oils, anthocyanins, and other phenolic constituents. Mangosteen (Garcinia Mangostana L) contains a class of naturally occurring polyphenolic compounds known as xanthone. Mangostin is a natural organic compound isolated from the mangosteen plant. It is a yellow colour, crystalline solid with a xanthone core structure. Raspberries (Rubus idaeus) are a diverse group of flowering plants that are closely related to blackberries. The anthocyanin molecule in raspberry consists of cyanidin and pelargonidin with glucose attached at the 3-position [14]. The pictures of the black plum, grapes skin, beetroot, mangosteen, and raspberry and the molecular structures of peonidin, cyanidin, betanin, mangostin, and pelargonidin are described in Figure 1.

![Fig 1. The pictures of the black plum, grapes skin, beetroot, mangosteen, and raspberry and the molecular structures of peonidin, cyanidin, betanin, mangostin, and pelargonidin.](image-url)
These extracted dyes were characterized by FT-IR and UV-Visible absorption spectra. The synthesis and characterization of N,N,N-tris-(2-methoxy-naphthalene-1-yl)·N,N,N-triphenylbenzene-1,3,5-triamine [MNTT] as hole transporting material was investigated in our previous work. And the fabrication of DSSC using MNTT as hole transporting compound and red sandal dye as photosensitizer was also reported [15]. Here, we reported on the fabrication of solid state dye-sensitized solar cells based on MNTT as hole transporting material and different natural dyes as photosensitizers. The conversion efficiencies (η) of the solar cells were calculated by the value of photocurrent density (Isc), open-current voltage (Voc), and fill factor (FF).

**EXPERIMENTAL**

**Measurements**

Ultraviolet-visible (UV-Vis) spectra were recorded as diluted solution in spectroscopic grade ethanol on a UV-Vis Shimadzu 1700 using 1.0 cm length quartz tube. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8400 spectrometer as potassium bromide (KBr) disc. Fluorescence spectra were recorded as diluted solution in spectroscopic grade ethanol on a PerkinElmer LS 45 fluorescence spectrometer using 1.0 cm length quartz tube. The metal contact electrode was deposited by thermal evaporation in UHV (5 × 10⁻⁶ mbar) using a Pfeiffer evaporator (Pfeiffer PLS 500s, Labor system). Evaporation rate was 0.28 nm/s. TiO₂ was coated on a transparent conducting oxide (TCO) plate using a spin coating machine. Coating was done with a programmable spin coater SCU 2008C (Apex Instruments Co., India). The substrate was spun up to a speed of 1000 rpm for 30 s with an acceleration of 200 rpm/s. The current-voltage (I-V) characteristics was monitored and measured by using a Keithley 276 source measurement unit. I-V measurements were generated using a self-written LabVIEW program. A solar simulator equipped with xenon lamp (AM 1.5, Solar Light Company, Model 16S-300, USA) was used as light source and light intensity was measured with a pyranometer (PMA2144, USA). The ultraviolet and infrared portion of the spectrum is eliminated by using a filter. The incident light intensity is tuned using neutral density filters (Eastman Kodak Company, USA).

**Preparation of TiO₂ electrode (photoanode)**

Fluorine-doped transparent conducting oxide (TCO), Degussa P25, and titanium sulphate were purchased from Sigma Aldrich. Solvent and chemicals were used as received. Highly fluorine-doped transparent conducting oxide (TCO) films deposited on glass (SnO₂:F) with resistance (30 µΩ) and thickness (1 mm) were first cleaned in a detergent solution using an ultrasonic bath for 15 minutes, rinsed with water and ethanol, and then dried. The structuring of the TCO was done using a chemical etching method. Zinc granulates were spread on the glass and reacted with HCl. The structured glass was then cleaned by ultrasonication in various solvents. Compact layers of TiO₂ were deposited on the TCO plate by spin coating method with area of 2 cm². It was prepared by precipitation of titanium sulphate using ammonium hydroxide. Then, water was added to this precipitate and stirred. 0.1 M HNO₃ was added to maintain pH (0.2) of the solution. The TCO was placed in a chamber for 1 minute and accelerated to a speed of 1000 rpm. 150 µl of TiO₂ solution was applied onto the substrate. The solution was allowed to set for about a minute on top for good penetration into the pores. The substrate was spun up to a speed of 1000 rpm for 30 s with an acceleration of 200 rpm/s. The samples were dried for 30 minutes. After deposition, the prepared TCO/TiO₂ was annealed at 100°C for 1 hour in air with a hot plate to achieve complete pyrolysis of organic species. The TiO₂ paste was made by mixing TiO₂ powder [Degussa P25] with ethanol and concentrated HCl. The paste was deposited onto TCO using doctor blade technique with area of 2.0 cm² and then sintered at 350°C for 30 minutes to burn out the organic additives and to get mechanically rugged samples.

**Preparation of natural photosensitizers**

**Extraction of dye from beetroot**

The beetroot was washed with water and vacuum dried at 60°C. The cleaned vegetable was chopped and soaked in 200 mL of absolute ethanol at room temperature in the dark for one week. Then, the residual parts were removed by filtration and the filtrate was washed with hexane several times to remove any oil or chlorophyll present in the extract. Then, the filtrates were concentrated at 40°C for use as sensitzers [16].
Extraction of dye from grapes

Freshly collected grapes were soaked in 150mL of 70% ethanol and stored overnight at 4°C. The extract mixed thoroughly and filtered to remove any solid residues. Subsequently, the extracts were centrifuged for five minutes to separate all residues. The supernatant of the ethanolic extracts was gently mixed with equal volumes of petroleum ether to separate polar and nonpolar pigments [17].

Extraction of dye from black plum

The clean fresh plum fruits were dried at 40°C and soaked into a 95% ethanol solution and kept in ambient temperature. Then, solid residues were filtrated and the natural dye solutions were concentrated at 40°C and purified by chromatogram method [18].

Extraction of dye from mangosteen

The method employed for macerating the crude mangosteen rinds powder was in 80% ethanol in water at room temperature for 24 hours, with occasional stirring. The solvent was removed to yield a concentrated extract. The ethanol extract was then dissolved in 50% methanol in water and partitioned 3-4 times in a separating funnel using n-hexane for 15 minutes each to remove non-polar compounds. The n-hexane phase was removed from the funnel and ethyl acetate was added to the methanol-water phase and shaken [19]. The addition of ethyl acetate was repeated 3-4 times. The ethyl acetate phase was collected and stored in an airtight plastic container protected from light.

Extraction of dye from raspberry

The fresh raspberries were washed with water and vacuum dried at 60°C. Then, they were chopped and immersed in absolute ethanol at room temperature in the dark for one week. Then, the solids were filtered out and the filtrates were concentrated at 40°C for use as sensitizers. The dye solutions were stored in the dark and refrigerated at 4°C.

After cooling to 80°C, the TiO₂ was immersed in ethanol solution of natural dyes for 12 hours.

Preparation of hole transporting material

\[ N,N,N\text{tris}(2\text{-methoxy-naphthalene-1-yl})-N,N,N\text{tri phenylbenzene-1,3,5-triamine} \] [MNTT] was synthesized and characterized [15]. The structure of MNTT as described in Figure 2.

![Structure of hole transporting material [MNTT]](image)

**Fig 2. Structure of hole transporting material [MNTT]**

In these DSSC, HTMs in THF (~800 nm) were deposited on the cell by spin coating method. The organic cells were kept overnight to allow maximum penetration of HTM in TiO₂.

Silver counter electrode

The metal electrode silver (200nm) was coated on HTM of DSSC by thermal evaporation.

**RESULTS & DISCUSSION**

Characterization of dyes

**IR spectra of dyes**

Black plum dye: 3415 cm⁻¹ (O-H stretching); 2933 cm⁻¹ (Aromatic C-H stretching); 2850 cm⁻¹ (methyl C-H stretching); 1448 cm⁻¹ (methyl C-H bending); 1259 cm⁻¹ (C-O-C stretching); and 1058 cm⁻¹ (C-O stretching).
Grapes dye: 3386 cm\(^{-1}\) (O-H stretching); 2937 cm\(^{-1}\) (aromatic C-H stretching); 1460 cm\(^{-1}\) (methyl C-H bending); and 1060 cm\(^{-1}\) (C-O stretching).

Raspberry dye: 3359 cm\(^{-1}\) (O-H stretching); 2960 cm\(^{-1}\) (aromatic C-H stretching); 1461 cm\(^{-1}\) (methyl C-H bending); and 1072 cm\(^{-1}\) (C-O stretching).

Mangosteen dye: 3404 cm\(^{-1}\) (O-H stretching); 2933 cm\(^{-1}\) (aromatic C-H stretching); 2852 cm\(^{-1}\) (methyl C-H stretching); 1448 cm\(^{-1}\) (methyl C-H bending); 1261 cm\(^{-1}\) (C-O-C stretching); and 1060 cm\(^{-1}\) (C-O stretching).

Beetroot dye: 3421 cm\(^{-1}\) (O-H stretching); 2925 cm\(^{-1}\) (aromatic C-H stretching); 1448 cm\(^{-1}\) (methyl C-H bending); 1053 cm\(^{-1}\) (C-O stretching); and 1263 cm\(^{-1}\) (C-N stretching).

**UV- Vis spectra of dyes**

We attempted to use five kinds of colourful natural dyes as sensitizers for DSSCs. Table 1 lists the UV-vis absorption data of the dyes extracted with ethanol. To investigate the absorption process of sunlight into dye, the UV-Vis measurement was performed between wavelength of 200 nm and 700 nm. The maximum absorption of each dye is listed in Table 1. These five dyes have better absorption features in the UV light zone. The absorption peaks of beetroot dye are at 478 nm and 540 nm. The anthocyanin dye extracted from different natural photosensitizer has different absorption peaks. The anthocyanin dye from grapes shows absorption at 529 nm, anthocyanin from raspberry shows two absorption peaks at 207 nm and 279 nm, and the absorption peaks of anthocyanin extracted from black plum are at 533 nm and 662 nm. The dye extracted from mangosteen absorbs at 378 nm. The ethanol extract of mangosteen pericarp showed various colours, whereas no obvious maximum absorption peak in the visible light region was observed. This result can be attributed to the superposition of absorption peaks. All dyes contained natural phenolic compounds. The chemical adsorption of these dyes is generally accepted because of the condensation of alcoholic-bound protons with the hydroxyl groups on the surface of nanostructured TiO\(_2\).[17]

**Fluorescence spectra of dyes**

Among the five natural dyes, the dyes extracted from raspberry and mangosteen show fluorescence peaks. Raspberry has three fluorescence peaks and fluorescence maximum at 636 nm. Mangosteen has two fluorescence peaks and fluorescence maximum at 763 nm. The light harvesting effect of dye plays an important role in capturing the photons and generating the electron/hole pair, as well as transferring them to the interface of the semiconductor and the electrolyte, respectively. The fluorescence material was absorbed on the TiO\(_2\) photo-electrode with sensitizers in dye-sensitized solar cell (DSSC) to enhance the photon-to-current efficiency. The improved light harvesting efficiency, which was achieved by the judicious choice/design of fluorescence material and sensitizing dyes, enhances the photovoltaic performance of the DSSCs.

**Photovoltaic properties of DSSC sensitized with natural dyes**

The dye sensitized solar cells based on raspberry, mangosteen, beetroot, black plum, and grapes are DSSC 1, DSSC 2, DSSC 3, DSSC 4, and DSSC 5, respectively. Photovoltaic tests of DSSC using these natural dyes as sensitizers were performed by measuring the current-voltage (I-V) characteristics under irradiation with white light (100 mW cm\(^{-2}\) from 300 W solar simulator). The performance of natural dyes as sensitizers in DSSC was evaluated by short circuit current (Isc), open circuit voltage (Voc), fill factor (FF), and energy conversion efficiency (\(\eta\)). The photovoltaic parameters of the DSSC are listed in Table 1.

**Table 1. Photo-electrochemical properties of dye sensitizes solar cell**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Absorption maximum [nm]</th>
<th>ISC [mA/cm(^2)]</th>
<th>VMAX [V]</th>
<th>IAX [mA/cm(^2)]</th>
<th>FF [%]</th>
<th>(\eta) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSSC1</td>
<td>534</td>
<td>1.88</td>
<td>1.5</td>
<td>1.25</td>
<td>0.50</td>
<td>0.94</td>
</tr>
<tr>
<td>DSSC2</td>
<td>378</td>
<td>0.49</td>
<td>1.75</td>
<td>0.35</td>
<td>0.63</td>
<td>0.31</td>
</tr>
<tr>
<td>DSSC3</td>
<td>478, 540</td>
<td>0.35</td>
<td>1.75</td>
<td>0.23</td>
<td>0.58</td>
<td>0.20</td>
</tr>
<tr>
<td>DSSC4</td>
<td>553, 662</td>
<td>0.27</td>
<td>1.75</td>
<td>0.20</td>
<td>0.65</td>
<td>0.18</td>
</tr>
<tr>
<td>DSSC5</td>
<td>529</td>
<td>0.09</td>
<td>1.75</td>
<td>0.06</td>
<td>0.58</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Different dyes show different photo conversion efficiency; that is, 0.94, 0.31, 0.20, 0.18, and 0.05 are DSSC 1, DSSC 2, DSSC 3, DSSC 4, and DSSC 5, respectively. Maximum 0.94% efficiency is obtained for raspberry dye.

Anthocyanins extracted from black plum, grape skin, and raspberry consist of an aromatic ring bonded to a heterocyclic ring containing an oxygen atom which in turn is linked by a C–C bond to a third aromatic ring; so, it may also be described as a C6–C3–C6 skeleton. The extended p conjugation, as well as the presence of positive charge and free -OH groups, allows the anthocyanins to absorb light in the visible region leading to a large variety of dye colours. The difference between anthocyanins of different types is mainly due to the number of hydroxyl and/or methoxy groups in the molecule. Due to this chemical complexity, there is a large variety of anthocyanins in nature and three anthocyanidins, i.e., cyanidin, pelargonidin, and peonidin are presented in our dyes. The number of hydroxyl and methoxyl groups determines the intensity, type, and stability of anthocyanins’ colour. Colour stability refers to the capacity of the molecule (dye) to maintain its colour properties. Generally, predominance of hydroxyl groups on the aromatic skeleton of anthocyanins gives rise to an intense blue colour while a red colour is observed when methoxyl groups prevail instead. Anthocyanine strongly absorb on the TiO2 as a result of a highly stable Ti4+-anthocyanin complex. The maximum absorption shown is grape dye, but raspberry dye (pelargonidin) has high efficiency. This is because raspberry dye shows fluorescence.

Betanins possess the carboxyl functional groups (-COOH) that is a key requisite to bind to the TiO2 nanostructure via the formation of ester-type linkage. Upon absorption of the dye onto the TiO2 surface, the proton of the carboxyl group is transferred to the oxide (e.g., TiO2). Contrarily, for anthocyanins the absorption onto TiO2 requires the presence of two ortho-hydroxyl groups that, on one hand leads to strong electronic coupling and a rapid electron transfer from the dye to the TiO2 and on the other hand also assists the back electron transfer (i.e., recombination process).

Mangostin extracted from mangosteen pericarp shows lesser absorption, but it contains methoxy and hydroxilic group that can help to better absorption on TiO2. Mangosteen has two fluorescence peaks and fluorescence maximum at 763 nm. The fluorescence material was absorbed on the TiO2 photo-electrode to enhance the photon-to-current efficiency.

CONCLUSION

Vegetable dyes are available in large quantity, easily and safely extracted from fruits, low in cost, and non-toxic. All these factors make the use of these natural products an intriguing challenge in the development of cheap and commercially available DSSCs. Organic dye-sensitized solid state solar cells were fabricated using synthesized HTM and different natural dyes. Different dyes show different photo conversion efficiency that varies from 0.94 to 0.05%. From the results, we can say that DSSC fabricated using raspberry shows high efficiency. In our previous report, the efficiency DSSC fabricated using red sandal dye was 0.25%. Raspberry, mangosteen, and red sandal show fluorescence peaks. Raspberry has three fluorescence peaks and fluorescence maximum at 636 nm. Mangosteen has two fluorescence peaks and fluorescence maximum at 763 nm. Red sandal has one fluorescence peak and fluorescence maximum at 536 nm. The fluorescence material was absorbed on the TiO2 photo-electrode with sensitizers in dye-sensitized solar cell (DSSC) to enhance the photon-to-current efficiency.

Instead of the ruthenium dye and back electrode gold, we have used the natural dyes and silver. These are the two major differences we adopted. We would like to highlight the total cost effect of the cell, which will be down to nearly 40% of a similar type of fabricated cell. The conversion of the non-conventional energy, even if for a very low percentage, is an advancement for mankind. The use of a lesser amount of chemicals is an added advantage when the natural dye is applied. This will be an introductory step to the green synthesis. The simple extraction procedure, low cost, and environmentally friendly natural dyes are promising sources of sensitizers for DSSCs.

REFERENCES

Synthesis of Diaryl and Arylalkyl Sulfides via Zinc-Catalyzed Thioetherification Reactions

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Abstract: A mild reaction protocol for zinc-catalyzed C-S cross-coupling reactions of aryl and alkyl thiols with aryl halides is reported. Due to the non-toxicity and large availability, zinc catalysts have undeniable significance over other catalytic systems. This triphenylphosphine-free protocol offers experimental simplicity and great functional group tolerance. A large number of aryl and alkyl sulfides have been successfully prepared in moderate to excellent yields by the reaction of differently substituted aryl halides with thiols.

Key Words: Transition metal catalysts; Cross-coupling reactions; Zinc catalyst; Aryl sulfides; C-S bond forming reactions.

INTRODUCTION

The construction of diarylthioether motifs has been a topic of immense interest for the past few years. This is due to the existence of the sulfide moiety in a large number of biologically and pharmacologically active compounds [1]. The presence of sulfur containing moieties in bioactive molecules offers subtle effects on their properties, as in the case of thio-nucleosides and thio-sugars [2]. There also exist a large number of commonly known antifungal agents with aryl sulfide moiety in their skeleton. Fenticonazole [3], ajoene [4], enediyne [5], and thiarubines [6] are some examples. A class of dianinodiphenylsulfones (DADS) [7] is well-known for their potent antibacterial activity against a variety of microorganisms. Diarylthioethers with heterocyclic motifs are the most commonly present structures in many drugs and are used for the treatment of diseases such as breast cancer [8], inflammatory diseases [9], HIV [10], and Alzheimer’s disease [11]. Owing to their great importance, a number of general methods are available for the synthesis of diarylthioethers. For example: the reduction of sulfones or sulfoxides, the coupling of metal thiolates and aryl iodides under elevated temperature, transition metal catalyzed cross-coupling reactions, etc. [12]. For the last few years, significant developments have been
realized in the field of transition metal catalyzed carbon-heteroatom bond-forming reactions [13]. Out of this, numerous methodologies have been introduced for the carbon-nitrogen and carbon-oxygen bond-forming reactions while that for carbon-sulfur bond formation is moderate. This is due to the deactivation of the metal catalysts by organosulfur reagents. The organosulfur reagents deactivate the metal catalysts by forming strong coordinate bonds with active metal centers. However, a wide array of transition metal catalysts are successfully utilized for the carbon-sulfur bond-forming reactions, comprising of palladium [14], copper [15], nickel [16], cobalt [17], iron [18], rhodium [19], indium [20], and zinc [21]. The first report on transition metal catalyzed carbon-sulfur bond formation was published by Migita et al. in 1978 using catalytic amount of tetrakis(triphenylphosphine) palladium complex [22].

RESULTS & DISCUSSION

Recently, we have reported the first zinc-catalyzed C-S cross-coupling reaction of aryl halides with aryl and alkyl thiols using Et₂Zn-L-proline catalytic system [21]. Herein, we report a detailed study on the zinc-catalyzed C-S cross-coupling reaction in presence of L-proline. We initiated the reaction by treating 4-iodoacetophenone (1a) with thiophenol (2a) in the presence of L-proline and K₂CO₃ in DME at 80 °C under nitrogen atmosphere (Scheme 1). After 20 hours of stirring, the solvent was removed under reduced pressure in a rotary evaporator and the product (3a) was separated from the crude reaction mixture by column chromatography on silica gel using EtOAc-hexane as the eluent to get a colourless solid.

Scheme 1. Zn-catalyzed C-S cross-coupling of 4-iodoacetophenone and thiophenol

The structure of the product (3a) was established by nuclear magnetic resonance, mass spectrometric, and other analyses. The ¹H NMR spectrum of the product showed a doublet (J = 8.4 Hz) for two protons at δ 7.83 corresponding to the two symmetric protons of the aromatic ring containing the acetyl group. The two protons appearing as a multiplet at δ 7.51-7.48 and the three protons appearing as a multiplet at δ 7.41-7.39 correspond to the protons of the unsubstituted aromatic ring. The doublet (J = 8.4 Hz) at δ 7.22 for two protons corresponds to the two symmetric protons of the aromatic ring containing the acetyl group. The three protons of the acetyl group appeared as a singlet at δ 2.55. In the ¹³C NMR spectrum, the carbonyl carbon resonated at δ 197.10 and the aromatic carbons resonated at δ 144.92-127.52. The methyl carbon resonated at δ 26.46. The IR spectrum showed an absorption at 3060 cm⁻¹ corresponding to the aromatic C-H stretching while that at 1669 cm⁻¹ is attributed to the C=O stretching. The C-S stretching appeared at 616 cm⁻¹. The HRMS of the compound (3a) also matched well with the calculated value. Moreover, all the spectral data were in good agreement with the reported values [23].

After having characterized the product, we decided to conduct optimization studies for the reaction in detail. For this, the most commonly available and simple ligands, La-Lf, were chosen for screening.

| Table 1. Ligand screening and catalyst loading studies |
|---|---|---|---|
| H₃COC | Et₂Zn (10 mol %) | K₂CO₃ (2 equiv.) | DME (3 ml) |
| 1a | Ligand (20 mol %) | 80 °C, 20 h |
| H₃COC | 2a | 3a |

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The ligand screening studies showed that L-proline (La) and 1,1'-bi-2-naphthol (Le) gave higher yield compared to other ligands (Table 1: Entries 1, 5). Ligands such as 2,2'-bipyridyl (Ld) and 1,10-phenanthroline (Lf) gave lower amount of the product (Table 1: Entries 6, 4), while simple ligands like ethylenediamine (Lb) and ethyleneglycol (Lc) afforded only trace amount of the product (Table 1: Entries 2, 3). Based on the above observations, we decided to choose L-proline as the ligand for the zinc-catalyzed C-S cross-coupling reaction since it is simple, easily available, and eco-friendly.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
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<tr>
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</tr>
<tr>
<td>2</td>
<td>Lb</td>
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</tr>
<tr>
<td>3</td>
<td>Lc</td>
<td>traces</td>
</tr>
<tr>
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<td>Ld</td>
<td>34</td>
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<td>5</td>
<td>Le</td>
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<tr>
<td>6</td>
<td>Lf</td>
<td>43</td>
</tr>
<tr>
<td>7b</td>
<td>La</td>
<td>53</td>
</tr>
<tr>
<td>8b</td>
<td>La</td>
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<td>La</td>
<td>19</td>
</tr>
<tr>
<td>10e</td>
<td>La</td>
<td>10</td>
</tr>
</tbody>
</table>

a: Isolated Yield, 
b: 8 mol% of Et₂Zn and 16 mol% of L-proline were used, 
c: 6 mol% of Et₂Zn and 12 mol% of L-proline were used, 
d: 4 mol% of Et₂Zn and 8 mol% of L-proline were used, 
e: 2 mol% of Et₂Zn and 4 mol% of L-proline were used

The catalyst loading studies were then conducted which showed that maximum yield was obtained when the catalyst loading was 8 mol% Et₂Zn and 16 mol% of L-proline (Table 1: Entry 7). Further reduction of the amount of the catalyst reduced the yield of the product appreciably (Table 1: Entries 1, 7-10).

After finding the optimal catalyst loading, we studied the influence of solvents in the coupling reaction. The results showed that both DME and acetonitrile are good solvents for this coupling reaction, since they gave comparatively good yield of the expected product (Table 2: Entries 3, 9-10, 14-16). In the presence of THF and BuOH as the solvents, the coupling took place with low yield of the product (Table 2: Entries 2, 5, 7-8). Next, we examined the influence of bases using both DME and acetonitrile as the reaction solvent. After screening different bases, it was revealed that bases such as K₂CO₃, NaO'Bu, Cs₂CO₃, and KO'Bu were better for the reaction (Table 2: Entries 3, 9-10, 14-16). NaH gave a lesser amount of the desired product (Table 2: Entries 12-13), while the organic base Et₃N did not afford any product (Table 2: Entry 11).

Many attempts to make the reaction complete by increasing the temperature were unsuccessful; low yield of the product was observed at elevated temperature (Table 2: Entry 17). No product was obtained when the reaction was carried out at room temperature (Table 2: Entry 18). Employing 1.5 equiv. of NaO'Bu as the base gave lower yield of the product (Table 2: Entry 19). When the reaction was performed without any base, no product could be observed (Table 2: Entry 20). Only traces of the product were detected in the absence of both Et₂Zn and L-proline (Table 2: Entry 21). When the reaction was carried out in the absence of inert atmosphere, the required product was obtained only in trace quantity (Table 2: Entry 22). From all these observations, it was concluded that the overall optimal condition for the desired zinc-catalyzed C-S cross-coupling reaction was a combination of 1 equiv. of 4-iodoacetophenone, 1.1 equiv. of thiophenol, 2 equiv. of NaO'Bu, 8 mol% of Et₂Zn, and 16 mol% of L-proline in acetonitrile at 80 °C under nitrogen atmosphere (Table 2: Entry 16).
Table 2. Optimization studies of zinc-catalyzed thioetherification reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (2 equiv.)</th>
<th>Solvent (3 ml)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<td>CH$_3$CN</td>
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</tr>
<tr>
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<td>NaO$t$Bu</td>
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<td>20</td>
<td>45</td>
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a: Reaction conditions: aryl iodide (1mmol), thiophenol (1.1 mmol), NaO$t$Bu (2 mmol), Et$_2$Zn (8 mol %), L-proline (16 mol %), 80 °C, 20 h; b: isolated yield; c: nd = not detected; d: 1.5 equiv. of NaO$t$Bu was used; e: Absence of both Et$_2$Zn and L-proline; f: Absence of inert atmosphere; g: Et$_2$Zn: L-proline (1:1).

Next, we explored the generality of the zinc-catalyzed C-S cross-coupling reaction using the newly developed optimal conditions. The reaction between differently substituted aryl halides and thiophenol was tested and the results are summarized in Table 3. The presence of electron-withdrawing groups on the aryl iodides afforded the respective sulfides in excellent yields (3a, 3c, 3e). But the electron-donating methoxy group on the aryl halide significantly lowered the yield of the product (3d). To our delight, the reaction worked well in the case of unsubstituted aryl iodide with simple thiophenol (3b). The protocol was then applied to aryl bromides, which also gave the sulfide product; but in low to moderate yields (Table 3: Entries 2, 6, 8). The methodology was then extended to aryl chloride, viz., 4-chloroacetophenone which afforded 33% of the sulfide (Table 3: Entries 3). We also attempted the reaction of ortho-substituted aryl halides with aryl thiols, which did not give isolable quantity of the product presumably due to steric reasons; but the product formation was detected in GC-MS.
Table 3. Substrate scope of zinc-catalyzed thioetherification reactions for substituted aryl halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Thiol</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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a: Reaction conditions: aryl halide (1 mmol), thiophenol (1.1 mmol), NaOBut (2 equiv.), Et₂Zn (8 mol %), L-proline (16 mol %), CH₃CN (3 ml), 80 °C, 20 h; b: isolated yield.

We then carried out the reaction between substituted thiophenols and aryl halides. It was observed that the electronic effects of the substituents on thiophenols have no considerable influence on the product yield. The thiophenol bearing electron-rich methoxy group at the C-4 position afforded the product with comparatively good yields (Table 4: Entries 1, 2, 4, 5). The thiophenol with methyl substituent at the C-4 position furnished moderate to good yield of the product (Table 4: Entries 7, 9, 11), while the C-4 fluoro-substituted thiophenol afforded good yields of the products (Table 4: Entries 12, 14). As anticipated, the substituted aryl bromides underwent cross-coupling reactions with 4-methoxy-, 4-methyl-, and 4-fluoro- substituted thiophenols affording the respective products in low yields (Table 4: Entry 3, 6, 8, 10, and 13). The meta-substituted aryl iodide gave only moderate yields of the product (Table 4: Entry 15).
Table 4. Substrate scope of zinc-catalyzed thioetherification reaction between substituted thiophenols and aryl halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Thiol</th>
<th>Product</th>
<th>Yield (%)b</th>
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a: Reaction conditions: aryl halide (1mmol), thiophenol (1.1 mmol), NaO\text{Bu} (2 mmol), Et$_2$Zn (8 mol %), L-proline (16 mol %), CH$_3$CN (3 ml), 80 °C, 20 h; b: isolated yield.
We then extended the reaction to alkyl thiols by conducting the reaction between aryl iodides and alkyl thiols under the optimal reaction conditions. As evident from Table 5, the protocol was tolerant towards many alkyl thiols. Benzyl thiol reacted smoothly with aryl iodides affording the desired product in good yield (Table 5: Entries 1, 2); but with 4-iodobenzonitrile as the coupling partner only moderate yield of the product could be obtained (Table 5: Entry 7). Notably, aliphatic thiols, such as n-butanethiol and i-propanethiol, also gave the corresponding products in moderate yields (Table 5: Entries 3-6). We also tried to extend this protocol to aryl iodides substituted with electron-releasing groups such as 4-iodotoluene and 4-iodoanisole; unfortunately, isolable quantity of the product could not be obtained although the product formation could be detected by GC-MS. In short, the new methodology works well in the case of aryl and alkyl thiols, including benzyl thiol with activated aryl iodides, allowing the facile preparation of a variety of sulfides in moderate to excellent yields.

Table 5. Substrate scope of zinc-catalyzed thioetherification reactions of alkyl thiols

<table>
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<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Thiol</th>
<th>Product</th>
<th>Yield (%)b</th>
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</tbody>
</table>

a: Reaction conditions: aryl iodide (1 mmol), thiophenol (1.1 mmol), NaO\text{Bu} (2 equiv.), Et\text{2}Zn (8 mol %), L-proline (16 mol %), CH$_3$CN (3 ml), 80 °C, 20 h; b: isolated yield.
Even though a detailed study is necessary to unravel the mechanistic pathway of the novel zinc-catalyzed C-S cross-coupling reaction, we propose a tentative mechanism, as shown below (Scheme 2). The reaction between Et₂Zn and L-proline would result in the in situ formation of a tetra-coordinated zinc-complex (I). This zinc-complex (I) can undergo oxidative addition with aryl halide by expelling one of the coordinated ligands, resulting in the generation of the Zn-complex (II). The complex (II) can then undergo ligand exchange with sodium thiolate, obtained by the deprotonation of thiophenol by NaO'Bu, forming the complex (III). The reductive elimination of the zinc-complex (III) would afford the thioether with the regeneration of the complex (I) and thus continues the catalytic cycle. The electron donating substituents on aryl halides significantly reduce the yield of the coupled product, presumably due to the sluggish oxidative addition of aryl halides with complex (I). However, an alternative route via the coordination of thiolate anion with Zinc-proline complex followed by the oxidative addition of aryl halide cannot be completely ruled out.

Scheme 2. A plausible catalytic cycle for the Zn-catalyzed C-S cross-coupling reaction
**CONCLUSIONS**

In summary, we have developed an efficient and promising protocol for the zinc-catalyzed S-arylation of aryl and alkyl thiols with differently substituted ary1 halides including iodides, bromides, and chlorides under mild reaction conditions. The in situ generated Et₂Zn-proline system in CH₃CN in the presence of NaO/Bu at 80 °C showed very good catalytic activity in the C-S cross-coupling reactions. The versatility and environmental friendliness of this method, in addition to the high yields it provides, makes it viable for use in organic synthesis. The newly developed Zn-proline catalytic system is an efficient and successful combination for the production of aryl and alkyl sulfides in high yields with 8 mol % of catalyst loading, and shows high functional group tolerance.

**EXPERIMENTAL SECTION**

Typical experimental procedure for the synthesis of 1-(4-phenylsulfanylphenyl)ethanone (3a): A dry sealed tube was charged with 1 mmol (246 mg) of 4-iodoacetophenone, 16 mol% of L-proline (18 mg), and 2 equiv. of NaO/Bu (192 mg) under nitrogen. To the above mixture was added 8 mol % of Et₂Zn (1M in hexane, 0.08 ml) and 3 ml of acetonitrile followed by the addition of 1.1 mmol of thiophenol (0.11 ml) under nitrogen. The sealed tube was heated in an oil bath which was preheated to 80 °C and the reaction mixture was stirred under the same conditions for 20 hours. The reaction mixture was then cooled and extracted with ethyl acetate (3 x 15 ml) and the ethyl acetate layer was washed with saturated aqueous NaCl solution (1 x 15 ml). The organic layer was dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure in a rotary evaporator. The crude residue was purified by column chromatography on silica gel using EtOAc-hexane as the eluent to get 217 mg (95 %) of the product as a colourless solid. M. P: 67 °C; 1H NMR (400 MHz, CDCl₃): δ 7.83 (d, J = 8.4 Hz, 2H), 7.51-7.48 (m, 2H), 7.21-7.39 (m, 3H), 7.22 (d, J = 8.4 Hz, 2H), 2.55 (s, 3H); 13C NMR (100 MHz, CDCl₃): δ 197.10, 144.92, 134.55, 133.87, 132.16, 129.69, 128.91, 128.79, 127.52, 26.46; IR (neat): 3060, 1669, 1555, 1182, 819, 616 cm⁻¹; HRMS (QToF): [M+H]+ calculated for C₁₅H₁₅NS is 229.0675

Diphenylsulfide (3b): Appearance: Colourless liquid; Yield: 149 mg (80 %); HRMS (QToF): [M+H]+ calculated for C₁₂H₁₂S is 187.0781; found 187.0799; Spectroscopic data were identical to those published previously [24].

4-Phenylsulfanylenzonitrile (3c): Appearance: Yellow liquid; Yield: 205 mg (97 %); HRMS (QToF): [M+H]+ calculated for C₁₃H₁₀NS is 212.0533; found 212.0526; Spectroscopic data were identical to those published previously [25].

1-Methoxy-4-phenylsulfanylenzenzene (3d): Appearance: Yellow liquid; Yield: 132 mg (61 %); HRMS (QToF): [M+H]+ calculated for C₁₃H₁₂O₃S is 216.0609; found 216.0603; Spectroscopic data were identical to those published previously [24].

1-Nitro-4-phenylsulfanylenzenzene (3e): Appearance: Yellow solid; MP: 55-57 °C; Yield: 199 mg (86 %); HRMS (QToF): [M+H]+ calculated for C₁₃H₁₀NO₃S is 232.0432; found 232.0426; Spectroscopic data were identical to those published previously [26].

1[4(4-Methoxyphenyl)sulfonylphenyl]ethanone (3f): Appearance: Colourless crystals; MP: 40 °C; Yield: 222 mg (86 %); HRMS (QToF): [M+H]+ calculated for C₁₅H₁₄O₄S is 259.0787; found 259.0783; Spectroscopic data were identical to those published previously [27].

4-Nitrophenyl-4-Methoxysulfide (3g): Appearance: Pale yellow crystals; MP: 65-67 °C; Yield: 183 mg (70 %); HRMS (QToF): [M+H]+ calculated for C₁₅H₁₂NO₃S is 262.0532; found 262.0539; Spectroscopic data were identical to those published previously [18c].

4-(4-Methoxyphenyl)sulfonylenzonitrile (3h): Appearance: Colourless solid; MP: 96-98 °C; Yield: 207 mg (86 %); HRMS (QToF) [M+H]+ calculated for C₁₅H₁₂O₅S is 242.0639; found 242.0627; Spectroscopic data were identical to those published previously [27].

1-(4-Tolylsulfanylphenyl)ethanone (3i): Appearance: Colourless solid; MP: 89-91 °C; Yield: 129 mg (53 %); HRMS (QToF): [M+H]+ calculated for C₁₅H₁₄O₃S is 243.0840; found 243.0844; Spectroscopic data were identical to those published previously [25].
4-Tolylsulfanylbenzonitrile (3j): Appearance: Colourless solid; MP: 100-102 °C; Yield: 146 mg (65 %); HRMS (QToF): [M+H]+ calculated for C11H14NS is 226.0846; found 226.0863; Spectroscopic data were identical to those published previously [28].

4-Nitrophenyl-4-toly sulfide (3k): Appearance: Pale yellow solid; MP: 79-81 °C; Yield: 201 mg (82 %); HRMS (QToF): [M+H]+ calculated for C26H2NO4S is 246.0589; found 246.0588; Spectroscopic data were identical to those published previously [25].

1-(4-Fluorophenylsulfanylphenyl)ethanone (3l): Appearance: Yellow liquid; Yield: 208 mg (85 %); HRMS (QToF): [M+H]+ calculated for C12H15NO3S is 247.0587; found 247.0589; Spectroscopic data were identical to those published previously [15d].

1-Nitro-4-fluorophenylsulfanylbenzene (3m): Appearance: Pale yellow solid; MP: 97-99 °C; Yield: 210 mg (85 %); HRMS (QToF): [M-H]- calculated for C13H9NO3S is 248.0181; found 248.0132; Spectroscopic data were identical to those published previously [16d].

1-Methoxy-4-trifluoromethylphenylsulfanylbenzene (3n): Appearance: Clear liquid; Yield: 190 mg (67 %); HRMS (QToF): [M]+ calculated for C13H13FO5S is 284.0482; found 284.0487; Spectroscopic data were identical to those published previously [15d].

1-(4-Benzy1sulfanyl)phenylethanone (3o): Appearance: Colourless solid; MP: 110-112 °C; Yield: 218 mg (90 %); HRMS (QToF): [M+H]+ calculated for C23H21OS is 243.0844; found 243.0839; Spectroscopic data were identical to those published previously [15d].

1-Benzylsulphonyl-4-Nitrobenzene (3p): Appearance: Yellow solid; MP: 97-99 °C; Yield: 196 mg (80 %); HRMS (QToF): [M+H]+ calculated for C11H14NO3S is 246.0589; found 246.0588; Spectroscopic data were identical to those published previously [29].

1-Butylsulfanyl-4-nitrobenzene (3q): Appearance: Pale yellow liquid; Yield: 125 mg (60 %); HRMS (QToF) [M+H]+ calculated for C10H13NO2S is 210.0588; found 210.0545; Spectroscopic data were identical to those published previously [29].

4-Butylsulfanylbenzonitrile (3r): Appearance: Pale yellow liquid; Yield: 107 mg (56 %); HRMS (QToF) [M+H]+ calculated for C11H14NS is 192.0846; found 192.0856; Spectroscopic data were identical to those published previously [29].

1(4-Butylsulfanyl)phenylethanone (3s): Appearance: Colourless liquid; Yield: 108 mg (52 %); HRMS (QToF) [M+H]+ calculated for C12H15OS is 209.0994; found 209.0992; Spectroscopic data were identical to those published previously [15d].

1-4-Propane-2-ylsulfanyl-phenylethan-1-one (3t): Appearance: Pale yellow liquid; Yield: 158 mg (70 %); HRMS (QToF) [M+H]+ calculated for C11H13OS is 195.0843; found 195.0849; Spectroscopic data were identical to those published previously [30].

4-Benzylsulfanylbenzonitrile (3u): Appearance: Yellow liquid; Yield: 158 mg (70 %); HRMS (QToF) [M+H]+ calculated for C14H12NS is 226.0684; found 226.0680; Spectroscopic data were identical to those published previously [16d].

ACKNOWLEDGEMENTS

GA thanks the Kerala State Council for Science, Technology, and Environment (KSCSTE), Trivandrum, India (Order no. 341/2013/KSCSTE dated 15.03.2013) for financial support. APT, SKS, and KKK thank the KSCSTE-India, UGC-India and the Ministry of Social Justice and Empowerment, India for research fellowships, respectively. We thank the Inter University Instrumentation Centre (IUIC) and Institute for Intensive Research in Basic Sciences (IIIRBS) of Mahatma Gandhi University for HRMS and NMR facilities, respectively.

REFERENCES

A Comparison of CYFRA 21-1, NSE, and CEA for the Serodiagnosis of Lung Cancer

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Abstract: There were 224,210 new cases of lung cancer in the US during 2014, and 159,260 died from lung cancer during that year [1]. Since early diagnosis and treatment leads to a better prognosis, the medical community is actively looking for new, non-invasive diagnostic tests for the disease. This includes the search for new and effective tumor markers. Tumor markers are used in combination with other tests to diagnose cancer. After the diagnosis, they are used to follow a patient’s case. The three tumor markers studied were neuron specific enolase (NSE), carcinoembryonic antigen (CEA), and CYFRA 21-1. In this study, the normal reference intervals were developed using sera from healthy adult donors. The analytical properties of the tumor marker assays were tested for and found to be satisfactory. The study was designed to compare the diagnostic and predictive values for the three tumor markers. Preliminary results on 638 patients (76 lung cancer patients, 562 healthy/non-cancer patients) included: (1) diagnostic % sensitivity (CEA: 22.37%, NSE: 0.00%, CYFRA 21-1: 18.92%), (2) diagnostic % specificity (CEA: 80.43%, NSE: 99.39%, CYFRA 21-1: 93.16%), (3) %PV+ (CEA: 13.39%, NSE: 4.17%, CYFRA 21-1: 28.00%), (4) %PV- (CEA: 88.45%, NSE: 95.83%, CYFRA 21-1: 90.90%), (5) % efficiency (CEA: 73.51, NSE: 86.65%, CYFRA 21-1: 84.00%). It was hypothesized that CYFRA 21-1 would be superior to CEA and NSE for the sero-diagnosis of lung cancer in a cohort of patients, and the hypothesis was rejected.

Key Words: Cancer, Carcinoembryonic Antigen, Neuron Specific Enolase, CYFRA 21-1, Lung Cancer.

INTRODUCTION

During the past 150 years, infectious diseases have been replaced by arterial disease and cancer as the major causes of death. Today, arterial disease accounts for 50% of all deaths in the US, and cancer accounts for 20% of deaths in the US. Heart attacks and strokes, which are associated with arterial disease, are seen as hazards of old age, lack of exercise, and poor diet. Cancer, though, is thought of as an unpredictable disease. It strikes no matter how old or how fit one is. This seems to be true because cancer can be related to environmental factors (Conklin, 1949) [2].

In the US, there were 1,665,540 cases of all types of cancer in 2014 and 585,720 deaths in 2014 (American Cancer Society, 2014) [1]. Since early diagnosis and treatment leads to a better prognosis, the medical community is actively looking for new non-invasive tests for the disease. This includes the search for new and effective tumor markers. The objective of this study was to compare and evaluate three tumor markers, CYFRA 21-1, carcinoembryonic antigen (CEA), and neuron specific enolase (NSE) for the sero-diagnosis of lung cancer.

The tumor marker CYFRA 21-1 is used to diagnose lung cancer, but it has also proven successful in identifying other tumors. It can be a marker for cancers of the head and neck. It also has proven successful in monitoring tumors of the cervix and has been considered useful in identifying non-small cell lung cancer (NSCLC). This includes squamous cell carcinoma (SCC), adenocarcinoma, and large cell carcinoma. These types of tumors account for 80% of the lung tumors (Nakamura & Wu, 1997) [3].

CEA is a marker that has been used for colorectal cancer, renal cancer, ovarian cancer, and breast cancer. It was first discovered in extracts of colon cancer. It was thought that a tumor specific marker had been found, but it was later discovered that not all colon tumors produced CEA. This is because tumors are very heterogeneous in their composition. Similarly, elevated blood CEA has been observed in heavy smokers who were tumor free. It is used
as a minor marker in lung cancer (Nakamura & Wu, 1997) [3].

NSE is a soluble metal-activated glycolytic metalloenzyme that provides components necessary for aerobic glycolysis. Decreasing values of this enzyme after primary treatment corresponding to the half-life period is the first sign of a good prognosis and good treatment effect. NSE can play no role in the staging of the disease. It was also found unable to differentiate between partial and complete response to treatment (Schneider et al., 2002) [4].

There were 224,210 new cases of lung cancer in the US during 2014, and 159,260 that died during 2014 (American Cancer Society, 2014) [1]. The incidence of lung cancer in western countries is directly proportional to the amount of cigarettes its inhabitants smoked 10 to 20 years earlier. The number of cigarettes smoked concomitantly in the western countries is completely irrelevant to the incidence of lung cancer during that time period. The damage has to have been done to the body years earlier than when the lung cancer first presents/occurs (Cairns, 1975) [5].

Just as the choice to smoke cigarettes influences the chance of someone developing lung cancer years later, a person’s occupational choice can have the same effect. Occupational cancers are those that are due to exposure to industrial chemicals (e.g., benzene) while working. These cancers may not appear until 10 to 20 years after the person has retired (Cairns, 1975) [5].

An area of importance when studying lung cancer is the method of diagnosis. Computed tomography is an important form of diagnosis and staging. Computed tomography scanning is based on the measurement of the amount of x-ray weakening as x-rays pass through different tissues within the body. Bone and tissues interact differently with the tomography, producing different attenuation coefficients. Attenuation coefficients characterize how easily a material or medium can be penetrated by a beam of light. Attenuation coefficients can be calculated as a function of the space in the cross sectional area where the x-rays pass. These different functions of space show up on the two-dimensional image as different shades of grey in an area. This creates a two-dimensional image and is generally used for chest x-rays and mammograms. If there is a tumor in the lung or in breast tissue, there will be a different attenuation coefficient as compared to that seen with normal lung and breast tissue. CT scanning is also a type of computed tomography. CT scanning is a cross sectional image obtained by exposure to a thin beam of x-rays throughout a 360 degree rotation. Both x-ray imaging and CT scanning provide exclusively anatomical information (Sherar, 2005) [6].

Another important form of diagnosis and staging is nuclear medicine and bone scans. Nuclear medicine uses radioactive agents to obtain images of tumors in the patient for diagnosis. The radioactive agents are radioactive isotopes. The radioactive isotopes used for diagnostic imaging emit high-energy photons. The photons are detected by a large sodium iodide crystal scanner, which transforms the photons into light signals. The light signals are then detected using a photomultiplier tube. This type of imaging is used commonly for detecting the presence of metastatic disease to the bone (Sherar, 2005) [6].

Magnetic resonance imaging (MRI) along with ultrasound can also be used for diagnosis and staging. Magnetic resonance imaging is based on magnetization of tissues when a patient is placed in a large, externally applied magnetic field contained in a MRI scanner. MRIs have become a commonly used technique for the diagnosis of cancer. MRIs have an excellent soft tissue contrast and resolution. It is excellent for imaging the brain, head, neck, and pelvic region (Sherar, 2005) [6].

The standard B mode ultrasound is used in diagnosis. The imaging projected from this ultrasound is based on the reflection of very high frequency sound signals. The ultrasound uses a piezoelectric crystal that generates a short ultrasound pulse that penetrates the tissue and is reflected by structures with different mechanical properties. The image the ultrasound forms is produced by time-gating the signals scattered back to the transducer. The scattering of ultrasound is different between normal tissues and tumors. An ultrasound is particularly useful for diagnosis in the abdomen and prostate. However, it will not pass through bone well enough for it to provide proper imaging the abdomen (Sherar, 2005) [6].

It was hypothesized that CYFRA 21-1 would be superior to CEA and NSE for the sero-diagnosis of lung cancer in a cohort of patients.

**MATERIALS & METHODS**

Two of the kits used in this project for the ELISA assays, carcinoembryonic antigen (CEA) and neuron specific enolase (NSE), were acquired from Diagnostic Automation, Inc. (Calabasas, CA). The third kit for the ELISA assay, CYFRA 21-1, was acquired from Fujirebio Diagnostic, Inc. /USA: Immuno-Biological Laboratories, Inc. (Seguin, TX). All the solutions that were used were
prepared using reagents and diluents present in the kits. Tests were performed using ELISA assays. Statistical analyses were performed using SPSS version 22 statistical software. Permission for this study was granted by the University of Southern Mississippi Institutional Review Board (protocol number 13042901) to ensure adherence to stipulated criteria.

Six hundred and thirty-eight patient serum samples were obtained from area hospitals with only a sample code number and the cancer diagnosis provided. Normal serum samples from two hundred and four healthy adult subjects were also obtained from area hospitals. All procedures protecting the confidentiality of the patients and subjects were followed. No information regarding the identification of a patient or subject was released by the hospitals involved. Aseptic techniques were used at all times with the samples. Blood samples were collected by hospital personnel at the respective hospitals, allowed to clot, and were separated before being frozen, given a code number, and packaged in plastic tubes for transport. Before testing, all of the samples were sorted into test tube racks and allowed to reach room temperature by soaking in a water bath at approximately 25°C.

Patient samples were classified by the hospital pathologists as either cancerous or cancer free based on histopathology (Table 1 and Table 7). This diagnosis was provided for comparison only. Similarly, healthy adult control subjects were determined to be disease free by their attending physicians (Table 6).

There were testing procedures included in the assay reagent kits which were followed for each assay (CEA, CYFRA 21-1, and NSE). The results of the assays performed were read with a Beckman Coulter AD 340 (Beckman-Coulter, Brea, CA, USA) microplate reader.

**CEA ELISA Assay Kit**

The kit’s reference number was 5201-16, and the lot# was DA314050802. The kits came from Diagnostic Automation/Cortez Diagnostics, Inc. (Calabasas, CA, USA). Other materials required that did not come in the kit were disposable tips, pipettors of 25 uL and 100 uL, a microwell reader, and deionized water for blanks.

The CEA quantitative test kit is based on a solid phase enzyme-linked immunosorbent assay with a detection range of 0-200 ng/mL. The test requires 15 uL of serum, and it performs with a specificity of 98.7% and sensitivity of 1.5 ng/mL per the manufacturer. The assay system utilizes one monoclonal anti-CEA antibody for solid phase immobilization and another mouse monoclonal anti-CEA antibody in the antibody-enzyme conjugate solution. The standards and the testing specimens were added to the CEA antibody coated microtiter wells. The CEA antibody labeled with horseradish peroxidase (conjugate) was added. If human CEA was present in the specimen, it would combine with the antibody on the well and the antibody conjugate. The solution was then washed with the wash buffer, which removed any unbound conjugate. The TMB solution was then added. A colorimetric reaction occurs whose final intensity reveals the concentration of CEA present (CEA Package Insert) [7].

When preparing the assay, all the reagents and samples were brought to room temperature (~25°C) and gently mixed. The wash buffer was prepared by adding 15 mL of the washing buffer into 735 mL of distilled water in a large flask. The mixture was capped and inverted several times to mix. The wash buffer was then poured into the wash solution bottle. Blanks (deionized water), calibration solutions, and controls were run in duplicate in the first 14 wells of each plate. The remaining wells contained serum samples and extra controls. A data sheet was kept to identify samples, calibrators, and controls with their locations [7].

**NSE ELISA Assay Kit**

The kit’s reference number was 6334-16, and the lot# was DA314050901. The kit came from Diagnostic Automation/Cortez Diagnostics, Inc. (Calabasas, CA, USA). Other materials required that did not come in the kit were disposable tips, pipettors of 25 uL and 100 uL, a microwell reader, and deionized water for blanks.

The NSE quantitative test kit is based on a solid phase enzyme-linked immunosorbent assay with a detection range of 0-200 ng/mL. The test requires 15 uL of serum, and it performs with a specificity of 98.7% and sensitivity of 1.5 ng/mL per the manufacturer. The assay system utilizes one monoclonal anti-NSE antibody for solid phase immobilization and another monoclonal anti-NSE antibody in the antibody-enzyme conjugate solution. The standards and the testing specimens were added to the antibody coated microtiter wells. If human NSE was present in the specimen, then it would combine with the antibody on the well and the antibody conjugate. The solution was then washed with the wash buffer, which removed any unbound conjugate. The amount of bound peroxidase (enzyme conjugate) was proportional to the concentration of the NSE present in each sample. After addition of the substrate and chromogen, the intensity of
blue color developed in proportion to the concentration of NSE antigen in the samples (NSE Package Insert) [8].

When preparing the assay, all the reagents and samples were brought to room temperature (~25°C) and gently mixed. The wash buffer was prepared by adding 15 mL of the washing buffer into 735 mL of distilled water in a large flask. The mixture was capped and inverted several times to mix. The wash buffer was then poured into the wash solution bottle. Blanks (deionized water), calibration solutions, and controls were run in duplicate in the first 14 wells of each kit. The remaining wells contained serum samples and extra controls. A data sheet was kept to identify samples, calibrators, and controls with their locations [9].

**CYFRA 21-1 ELISA Assay Kit**

The kit’s number was 211-10, and the lot# was 34112-1. The kits came from Fujirebio Diagnostic, Inc./USA: Immuno-Biological Laboratories, Inc. (Seguin, TX). Other materials required that did not come in the kits were disposable tips, pipettors of 25 uL and 100 uL, a microwell reader, and deionized water for blanks.

The CYFRA 21-1 quantitative test kit is based on a solid phase enzyme-linked immunosorbent assay with a detection range of 0.5-50 ng/mL. The test sensitivity was 0.12 ng/mL and the % specificity was 98% per the manufacturer. The assay system utilizes one monoclonal anti-CYFRA 21-1 antibody for solid phase immobilization and another mouse monoclonal antibody conjugate in the antibody-enzyme conjugate solution. The standards and the testing specimens were added to the CYFRA 21-1 antibody coated microwell wells. The CYFRA 21-1 antibody labeled with horseradish peroxidase (conjugate) was added. If human CYFRA 21-1 was present in the specimen, then it would combine with the antibody on the well and the antibody conjugate. The solution was then washed with the wash buffer, which removed any unbound conjugate. The TMB solution was then added. A colorimetric reaction occurs whose final intensity reveals the concentration of CYFRA 21-1 present (Cyfra 21-1 Package Insert) [9].

When preparing the assay, all the reagents and samples were brought to room temperature (~25°C) and gently mixed. The wash buffer was prepared by adding 50 mL of the washing buffer into 1200 mL of distilled water in a large flask. The mixture was capped and inverted several times to mix. The wash buffer was then poured into the wash solution bottle. Blanks (deionized water), calibration solutions, and controls were run in duplicate in the first 14 wells of each kit. The remaining wells contained serum samples and extra controls. A data sheet was kept to identify samples, calibrators, and controls with their locations [9].

**Table 1. Patient Sample Classification**

<table>
<thead>
<tr>
<th>Number of Samples</th>
<th>Cancer Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>76</td>
<td>Cancerous</td>
</tr>
<tr>
<td>562</td>
<td>Cancer Free</td>
</tr>
<tr>
<td><strong>Total number of Patients</strong>: 638</td>
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**RESULTS**

Over the course of the project, there were NSE, CEA, and CYFRA 21-1 quality control samples incorporated into the assays to determine within-run and between-run precision (Tables 2-3). These controls had a known amount of antigen incorporated into the control sample. This determined if the assay was performing correctly. With a percent coefficient of variation (% CV) of less than 10% all three markers had excellent within-run precision (Table 2). Similarly, the between-run precision was excellent for CYFRA 21-1 and CEA but only good for NSE (15.37%) (Table 3).

Serial dilutions of patient samples were used to determine the linearity of the assays (Table 4). These results indicate excellent linearity with R² values between 0.94 and 0.99.

The minimum concentration each assay was able to detect (analytical sensitivity) was determined by assaying replicates of a control with no antigen (zero control) and calculating the mean (+/-) two standard deviations (̄X +/- 2SD) (Table 5). Values less than the high end of the range are considered to have no antigen or a value of zero. The analytical sensitivity of NSE was 7.02 ng/mL and those for CYFRA 21-1 and CEA had cut off values of less than 1.0 ng/mL (Table 5).

The normal reference intervals (̄X +/- 2SD) are the reference intervals that were developed from healthy adult control subjects. The healthy adult control subjects were known to have no disease. The normal reference intervals for each of the antigens studied can be seen in Table 6. For tumor markers, the high end of the range represents a possible cut-off value between “presumed healthy” (negative for disease) and “presumed cancerous” (positive for disease). The low end of the range is assumed to imply healthy. Since a variety of factors (e.g. age,
Diagnostic sensitivity is the proportion of individuals with a disease who test positive for the disease. The higher the sensitivity the better the test is. Diagnostic specificities of 0.00% (NSE), 18.92% (CYFRA 21-1), and 22.37% (CEA) were obtained (Table 7), suggesting that CEA was slightly better than CYFRA 21-1 and that NSE was not useful. Diagnostic specificity is the proportion of individuals without the disease who test negatively for the disease. Diagnostic specificities of 99.39% (NSE), 93.16% (CYFRA 21-1), and 80.43% (CEA) were obtained. Here the values for NSE were superior and those of CEA and CYFRA 21-1 were excellent (Table 7). Some other parameters that can be evaluated are positive predictive value (PV+ %), negative predictive value (PV- %), and percent efficiency (Efficiency %). Positive predictive value is the fraction of positive tests that are true positives. Negative predictive value is the fraction of negative tests that are true negatives. The percent efficiency is the fraction of all test results that are either true positives or true negatives. The positive predictive values are low, whereas the negative predictive values are high for all three assays. The percent efficiencies are good, as well, for the three assays (Table 7).

Table 2. Within Run Assay Precision for NSE, CYFRA 21-1, and CEA

<table>
<thead>
<tr>
<th></th>
<th>Mean (ng/mL)</th>
<th>SD</th>
<th>%CV</th>
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<tbody>
<tr>
<td>NSE control</td>
<td>10</td>
<td>7.55</td>
<td>0.21</td>
</tr>
<tr>
<td>CYFRA 21-1 High Control</td>
<td>20</td>
<td>14.17</td>
<td>0.77</td>
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<tr>
<td>CYFRA 21-1 Low Control</td>
<td>20</td>
<td>4.41</td>
<td>0.28</td>
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<tr>
<td>CEA High Control</td>
<td>40</td>
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<tr>
<td>CEA Low control</td>
<td>43</td>
<td>4.28</td>
<td>0.29</td>
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</table>

Table 3. Between Run Precision for NSE, CYFRA 21-1, and CEA

<table>
<thead>
<tr>
<th></th>
<th>Mean (ng/mL)</th>
<th>SD</th>
<th>%CV</th>
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</thead>
<tbody>
<tr>
<td>NSE control</td>
<td>43</td>
<td>7.87</td>
<td>1.21</td>
</tr>
<tr>
<td>CYFRA 21-1 High Control</td>
<td>76</td>
<td>13.97</td>
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<tr>
<td>CYFRA 21-1 Low Control</td>
<td>78</td>
<td>4.45</td>
<td>0.50</td>
</tr>
<tr>
<td>CEA High Control</td>
<td>72</td>
<td>62.64</td>
<td>3.40</td>
</tr>
<tr>
<td>CEA Low control</td>
<td>76</td>
<td>4.44</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Table 4. Assay Linearity for NSE, CYFRA 21-1, and CEA

<table>
<thead>
<tr>
<th>Assay</th>
<th>R squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE</td>
<td>0.997</td>
</tr>
<tr>
<td>Cyfra 21-1</td>
<td>0.992</td>
</tr>
<tr>
<td>CEA</td>
<td>0.939</td>
</tr>
</tbody>
</table>

Table 5. Analytical Sensitivity for NSE, CYFRA 21-1, and CEA

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean (ng/mL)</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE</td>
<td>10</td>
<td>6.56</td>
<td>0.23</td>
<td>6.10-7.02</td>
</tr>
<tr>
<td>CYFRA 21-1</td>
<td>20</td>
<td>0.01</td>
<td>0.03</td>
<td>0.00-0.07</td>
</tr>
<tr>
<td>CEA</td>
<td>20</td>
<td>0.00</td>
<td>0.35</td>
<td>0.00-0.70</td>
</tr>
</tbody>
</table>

Table 6. Normal Reference Intervals for NSE, CYFRA 21-1, and CEA

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE</td>
<td>174</td>
<td>3.62</td>
<td>8.45</td>
<td>6.61</td>
<td>1.31</td>
<td>3.99-9.23</td>
</tr>
<tr>
<td>CYFRA 21-1</td>
<td>189</td>
<td>0.00</td>
<td>82.9</td>
<td>2.21</td>
<td>9.36</td>
<td>0.00-20.93</td>
</tr>
<tr>
<td>CEA</td>
<td>204</td>
<td>0.00</td>
<td>16.10</td>
<td>2.40</td>
<td>2.63</td>
<td>0.00-7.66</td>
</tr>
</tbody>
</table>

Table 7. Predictive values for NSE, CYFRA 21-1, and CEA in 638 Patients

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PV+ (%)</th>
<th>PV- (%)</th>
<th>Efficiency (%)</th>
<th>Cut-Off (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE</td>
<td>0.00</td>
<td>99.39</td>
<td>4.17</td>
<td>87.12</td>
<td>86.65</td>
<td>15.01</td>
</tr>
<tr>
<td>CYFRA 21-1</td>
<td>18.92</td>
<td>93.16</td>
<td>28.00</td>
<td>89.09</td>
<td>84.00</td>
<td>1.82</td>
</tr>
<tr>
<td>CEA</td>
<td>22.37</td>
<td>80.43</td>
<td>13.39</td>
<td>88.45</td>
<td>73.51</td>
<td>5.01</td>
</tr>
</tbody>
</table>

DISCUSSION

The analytical parameters for each of the three testing methods were good. The normal reference interval for CYFRA 21-1 was dramatically higher than the reference interval determined by the manufacturer. This is possibly due to geographic location and consequently the mix of healthy adult subjects tested. None of the diagnostic sensitivities were optimal, but of the three examined, CEA was the best predictor of the disease. The sensitivity...
would be the most important test result because it demonstrates the ability of the assay to diagnose the presence of disease. The diagnostic specificities obtained for the true negatives were excellent, with NSE having the best specificity at 99.39%. This result greatly differed from the 0% found for the sensitivity of NSE. Mathematically, because of the high percent efficiency of NSE at 86.65%, it appeared to be the best predictor of the disease, but with a diagnostic percent sensitivity of 0%, NSE is only useful to exclude disease. The cut-off points used for all three of the markers were those of the manufacturers. By adjusting the cut-off points one could raise the diagnostic percent sensitivity, but the diagnostic percent specificity would be concomitantly lowered. The manufacturers recommend that each laboratory should determine its own normal/healthy and abnormal/unhealthy ranges so as to account for any environmental factors such as diet or climate and/or the genetic mixtures of patients seen in the area. In this case, changing the cut-off points did not significantly improve the results (data not shown).

A strong point of this study is the small number of people who were directly involved in the testing of the samples. This keeps the relative amount of human error minimal. The age of some of the samples is a possible weakness due to potential sample degradation at minus 20°C. To improve the accuracy of the study, a larger number of subjects could be obtained, and the subjects could be acquired from multiple geographic regions. The samples should also be fresh and only thawed once when tested.

From the data collected, CEA was the most sensitive marker for predicting lung cancer. NSE was the most specific, and CYFRA 21-1 had the next highest sensitivity and specificity. The highest sensitivity is the most important part of a test because it predicts the true positives. CEA, the best predictor of the disease, is one of the oldest tumor markers. It is commonly used in determining other cancers such as colorectal cancer. The CEA subgroup members are cell membrane associated and show a complex expression pattern in normal and cancerous tissues (Hammarstrom, 1999) [10]. This is a strong point for the tumor marker because it has the ability to track cancer formation in different areas of the body in different organs. One objective of a tumor marker is to serve as a non-invasive test to track a patient’s health (remission vs relapse) after recovery from cancer. Physicians and researchers are always seeking non-invasive tests, like tumor markers, to make early diagnosis and track a patient’s recovery. While arguably it came in a close second, the hypothesis that CYFRA 21-1 would be the most sensitive and specific predictor of lung cancer was rejected because CEA had a higher sensitivity than CYFRA 21-1. However, CYFRA 21-1 is an independent prognostic factor that is useful in the earlier stages of squamous cell lung cancer (SQC) (Kulpa, 2002) [11].

REFERENCES

REVISITING NEWLANDS’ LAW OF OCTAVES:
TUNING IN ON TRANSITION METALS

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Key Words: Transitional metals; Law of octaves; Newlands

Chemistry and Music have many connections in both practice and practitioners. Both have layered complexities underpinned by harmonics and mathematical roots [1]. Where music has its octave, chemistry has its octet. Famous in both fields, Alexander Borodin is known for composing “In the Steppes of Central Asia” and for a posthumous Tony award from his music used in a Broadway musical some two-thirds of a century after his death. He is also credited, along with Charles Wurtz [2], with independent co-discovery of the aldol condensation in 1872 while working with Emil Erlenmeyer. During Borodin’s time in Germany, he met Dmitri Mendeleev before the fellow Russian unveiled his “periodic system” in 1869 that would become the foundation of the periodic table.

In 1865, English chemist John Newlands had divided 62 known elements into eight groups based on similar properties and published “On the Law of Octaves” [3]. As the inert gases were not known at this stage, it is easy, with hindsight, to see that every eighth element would have been in the same family up until the transition metals. This pitfall with transition metals (Fig. 1) meant Newlands’ initial findings were dismissed by the Society of Chemists (forerunner to the RSC) but he was eventually recognized with the Davy Medal in 1887. Yet, there is in fact a connection between piano scales and the transition metals that may be useful in teaching students the commonalities of the periodic table.

Fig 1. Musical representation of Newlands’ Law of Octaves (Source “Chemistry and All that Jazz” [4], reproduced with permission)
An octave is only seven steps as the first and eighth notes are repeated: if middle C is note 1, the 8th note is also C. However, beyond the eight ivory notes of the C major scale, there are five ebony notes that lay untouched. These represent unfilled d orbitals, if you will. Again, starting from middle C as note 1, the 18th note in the C major scale is an F. However, starting again from middle C but playing every note (C, C#, D, D#, and so on), the 18th note is also an F but one octave lower (Fig. 2). This also works starting from A, B, D, E or G (but not F).

![Figure 2. Two 18-note patterns starting from middle C arriving an octave apart. Top numbering indicates playing every note, bottom follows C major scale.](image)

Thus, the initial failing of the Law of Octaves to incorporate transition metals has a fairly simple musical solution. Using either an octave or the aforementioned “octadecave” (Fig. 2) may be useful in promoting understanding of the periodic table, not only in introductory chemistry but to the general public, as well. If an actual piano is available, it is ideal as the very sound of the note itself is generated by a combination of first row and transition elements: high carbon steel piano wire.

References


**Note:** The author’s father, Prof. Oliver C. Houston, Jr., taught organ and music theory at Graceland University in Lamoni, Iowa, for over 48 years. This article is dedicated to his memory.
Longtime Fellows of the AIC

Veteran Chemist - Dr. Lawrence Duffy

Mary van Muelken
Resilience and Adaptation Program, University of Alaska Fairbanks, Fairbanks, Alaska
(Email: mavanmuelken@alaska.edu)

Dr. Lawrence Duffy is a veteran chemical scientist and educator, a long time Fellow of The American Institute of Chemists, and an active member of the Editorial Review Board of The Chemist. Dr. Duffy received his BS in chemistry from Fordham University in 1969 and an MS in organic chemistry from the University of Alaska in 1971. Following three years of service in the US Navy, Lieutenant Duffy returned to the University of Alaska and completed his PhD degree in biochemistry in 1977. After several years of research at Boston University, the Roche Institute of Molecular Biology, the University of Texas Medical Branch, Galveston, and Harvard Medical School, Dr. Duffy returned to the University of Alaska where he has held numerous administrative positions and continues to teach biochemistry, general chemistry, and research ethics.

Dr. Duffy has broad research interests ranging from neurochemistry and biochemistry to environmental health. While at Harvard Medical School, Dr. Duffy worked with noted neuroscientist Dr. Denis Selkoe on elucidating the structure of Alzheimer’s amyloid. On returning to the University of Alaska Fairbanks, he continued his amyloid studies using synthetic peptides to characterize their neurotoxicity in collaboration with neuroscientists Bruce Yankner and Dan Kirchner. He additionally initiated studies on the effect of the extreme seasonality of the far north by studying melatonin diurnal cycles in both humans and their companion sled dogs.

Working with environmental and wildlife biologists, Dr. Duffy introduced the use of common human biomarkers into the studies of mammals impacted by the Exxon Valdez oil spill. His studies demonstrate that chronic exposure can be measured biochemically in mammals, not only showing damage to a resource, but also demonstrating ecosystem recovery. His research also focuses on the development of biomarker and animal models as sentinel species. Dr. Duffy’s work on mercury in subsistence food is used by policy makers on the national level and allows him to involve students in research and discussions of environmental issues related to environmental
ethics and justice. Current research projects include developing a dog model as a sentinel species for the Arctic to determine the effects of mercury on cytokine signaling, as well as environmental monitoring of long range transport of pollutants and their impact on subsistence resources.

After holding the administrative positions of Department Head and Associate Dean for Graduate Studies and Outreach in the College of Science Engineering and Mathematics, he became Dean of the Graduate School and Interdisciplinary Programs. Currently, as Director of the Resilience and Adaptation Program, an interdisciplinary graduate program, Dr. Duffy seeks to develop an Alaskan workforce well-versed in resilience, sustainability, adaptation and social-ecological (human-natural) systems research. In recent years, RAP students have become leaders in academia, state and federal agencies, as well as tribal and non-profit organizations. Dr. Duffy serves as the Principal Investigator for a National Science Foundation S-STEM award, *Resilience and Adaptation in Environmental and Natural Science*. This undergraduate component to the Resilience and Adaptation Program supports underrepresented students engaged in scientific research.

An innovative educator, Dr. Duffy has been a strong proponent of the Science Education for New Civic Engagements and Responsibilities (SENCER) for many years. He is an advocate for place-based learning and has a deep appreciation for Alaska Native Traditional Ecological Knowledge (TEK). Dr. Duffy initiated a partnership with the Effie Kokrine Early College Charter School and teaches university level chemistry courses to high school students. These dual credit courses help students acclimate to university expectations early while retaining a supportive high school laboratory environment. During the summer months, Dr. Duffy teaches Chemistry to Rural Alaska Honors Institute students. Following his RAHI instruction, he can often be found in Barrow, Alaska, participating in Ilisagvik Tribal College’s Climate Change Camps.

Dr. Duffy has received the American Chemical Society’s Stanley C. Israel Award for Advancing Diversity in the Chemical Sciences, the National Institute for Deaf and Communication Disorders Minority Mentoring Award, the UAF Chancellor’s Award for Diversity and the Usibelli Distinguished Research Award. He is a fellow of the Arctic Institute of North America and the American Institute of Chemistry, where he served as President in 2004. He serves as the Executive Director of the Arctic Division, American Association for the Advancement of Science.
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3. To be diligent in exposing and opposing such errors and frauds as The Chemist’s special knowledge brings to light;
4. To sustain the institute and burdens of the community as a responsible citizen;
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6. To use only honorable means of competition for professional employment; to advertise only in a dignified and factual manner; to refrain from unfairly injuring, directly or indirectly, the professional reputation, prospects, or business of a fellow Chemist, or attempting to supplant a fellow chemist already selected for employment; to perform services for a client only at rates that fairly reflect costs of equipment, supplies, and overhead expenses as well as fair personal compensation;
7. To accept employment from more than one employer or client only when there is no conflict of interest; to accept commission or compensation in any form from more than one interested party only with the full knowledge and consent of all parties concerned;
8. To perform all professional work in a manner that merits full confidence and trust; to be conservative in estimates, reports, and testimony, especially if these are related to the promotion of a business enterprise or the protection of the public interest, and to state explicitly any known bias embodied therein; to advise client or employer of the probability of success before undertaking a project;
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13. To report any infractions of these principles of professional conduct to the authorities responsible for enforcement of applicable laws or regulations, or to the Ethics Committee of The American Institute of Chemists, as appropriate.
Manuscript Style Guide

The Chemist is the official online refereed journal of The American Institute of Chemists (AIC). We accept submissions from all fields of chemistry defined broadly (e.g., scientific, educational, socio-political). The Chemist will not consider any paper or part of a paper that has been published or is under consideration for publication anywhere else. The editorial office of The Chemist is located at: The American Institute of Chemists, Inc. 315 Chestnut Street Philadelphia, PA 19106-2702, Email: aicoffice@theaic.org.

Categories of Submissions

RESEARCH PAPERS

Research Papers (up to ~5000 words) that are original will only be accepted. Research Papers are peer-reviewed and include an abstract, an introduction, up to 5 figures or tables, sections with brief subheadings and a maximum of approximately 30 references.

REPORTS

Reports (up to ~3000 words) present new research results of broad interest to the chemistry community. Reports are peer-reviewed and include an abstract, an introductory paragraph, up to 3 figures or tables, and a maximum of approximately 15 references.

BRIEF REPORTS

Brief Reports (up to ~1500 words) are short papers that are peer-reviewed and present novel techniques or results of interest to the chemistry community.

REVIEW ARTICLES

Review Articles (up to ~6000 words) describe new or existing areas of interest to the chemistry community. Review Articles are peer-reviewed and include an abstract, an introduction that outlines the main point, brief subheadings for each section and up to 80 references.

LETTERS

Letters (up to ~500 words) discuss material published in The Chemist in the last 8 months or issues of general interest to the chemistry community.

BOOK REVIEWS

Book Reviews (up to ~ 500 words) will be accepted.
Manuscript Preparation

RESEARCH PAPERS, REPORTS, BRIEF REPORTS & REVIEW ARTICLES

- The first page should contain the title, authors and their respective institutions/affiliations and the corresponding author. The general area of chemistry the article represents should also be indicated, i.e. General Chemistry, Organic Chemistry, Physical Chemistry, Chemical Education, etc.

- Titles should be 55 characters or less for Research Papers, Reports, and Brief Reports. Review articles should have a title of up to 80 characters.

- Abstracts explain to the reader why the research was conducted and why it is important to the field. The abstract should be 100-150 words and convey the main point of the paper along with an outline of the results and conclusions.

- Text should start with a brief introduction highlighting the paper’s significance and should be understood to readers of all chemistry disciplines. All symbols, abbreviations, and acronyms should be defined the first time they are used. All tables and figures should be cited in numerical order.

- Units must be used appropriately. Internationally accepted units of measurement should be used in conjunction with their numerical values. Abbreviate the units as shown: cal, kcal, µg, mg, g (or gm), %, °C, nm, µm (not m), mm, cm, cm³, m, in. (or write out inch), h (or hr), min, s (or sec), ml [write out liter(s)], kg. Wherever commonly used units are used their conversion factors must be shown at their first occurrence. Greek symbols are permitted as long as they show clearly in the soft copy.

- References and notes should be numbered in the order in which they are cited, starting with the text and then through the table and figure legends. Each reference should have a unique number and any references to unpublished data should be given a number in the text and referred to in the references. References should follow the standards presented in the AIC Reference Style Guidelines below.

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References should be cited as numbers within square brackets [] at the appropriate place in the text. The reference numbers should be cited in the correct order throughout the text (including those in tables and figure captions, numbered according to where the table or figure is designated to appear). The references themselves are listed in numerical order at the end of the final printed text along with any Notes. Journal abbreviations should be consistent with those presented in Chemical Abstracts Service Source Index (CASSI) (http://www.cas.org) guide available at most academic libraries.
• **Names** and initials of all authors should always be given in the reference and must not be replaced by the phrase *et al.* This does not preclude one from referring to them by the first author, *et al* in the text.

• **Tables** should be in numerical order as they appear in the text and they should not duplicate the text. Tables should be completely understandable without reading the text. Every table should have a title. Table titles should be placed above the respective tables.

  Table 1. Bond Lengths (Å) of 2-aminophenol

• **Figure legends** should be in numerical order as they appear in the text. Legends should be limited to 250 words.

  Figure 1. PVC Melt Flow Characterized by Analytical Structural Method

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