

# Conjugation reactions of hybrid organosilanes for nanoparticle and surface modifications

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## ABSTRACT

Hybrid Molecules with incorporation of heteroatoms and different domains and properties could be achieved by the use of Silanes, Organosilanes, and chemically functionalized Organosilanes. These chemical agents are versatile reagents that could be covalently linked to other types of molecules such as Organics by covalent and non-covalent linking. In this way, in this Research communication was summarized and discussed the use of a set of modified Organosilanes based on different experimental reactions for targeted objectives. Different conjugation reactions were involucrated based on optimized current Organic chemical reactions. By this manner, it was showed the chemical modifications of Organosilanes with Fluorescent dye reporters. As example, it was afforded the use of these bi-functional chemical species, with hydrolysable hetero-atom bonds accompanied with Laser dyes sensitizer properties. Thus, it was showed their applications for design and synthesis of Nanoparticles and chemical surface modifications.

**Keywords:** Laser dye reporters, Organosilanes, Bioconjugation, conjugation reactions, Covalent and non-covalent bonding.

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## Introduction

Silicon as the second most abundant element on earth after oxygen with a similar electronic configuration as Carbon (Smith, 1972) showed to be largely used and developed in Chemistry by Silane compounds and derivatives (Petkowski, 2020). From these groups of compounds then it was developed modified Silanes such as Organosilanes (Thames, 1996) that today are as well applied in a huge number of studies and developments within Chemistry, Biochemistry, Nano-technology, Biotechnology, etc. For example, Organosilanes showed a high impact on Polymerization reactions with incorporation of different types of molecules (Tau, 2011), Biomolecules, formation of porous structures (Maria Chong, 2004), and Functionalities (Liu, 2018). Moreover, the capability to polymerize lead to the formation from variable small chemical oligomeric structures, to modified Polymers that in controlled conditions formed Nanoparticles (Ab Rahman, 2012 and Fernandes, 2019).

In similar manner, Organosilanes were applied for Chemical surface modifications (Brehm, 2020) that led to further Chemical functionalization for different types of studies and applications (Nejhad, 2015). In this way, in literature it could be found a lot of studies and developments with the use of Organosilanes that in combination of other types of reactions could generate functional materials with a wide view of uses, interests and applications depending of the modifications achieved.

Thus, it was afforded the use of Organosilanes, and modified Organosilanes for Hybrid Organic and Inorganic Nanomaterials synthesis with incorporation of Fluorescent Laser dyes. In this manner, based in designs and synthesis reported by us as well from other authors it was showed the versatility of these Luminescent Nanomaterials. In this context, it was discussed the main Organic chemical reactions used for covalent linking and Bioconjugation in the design of Nanomaterials and functional modified surfaces.

*Classical conjugations reactions based organic chemistry*  
There are a larger types reactions that it could be applied for covalent bonding; however not so many within aqueous solutions and Colloidal dispersions.

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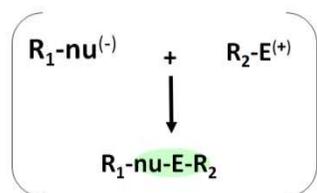
The reactions should be compatible as well for the targeted applications. In this way, as for example for Bio-applications it is highly desired biocompatible conditions to avoid problems in their use. Thus, within these groups of reactions, there are many types of reactions developed in variable polar media, with organic, aqueous and mixed solvents. For example there were many chemical reactions based on differences in the electronic densities of heteroatoms and Organic functional groups. In this manner, nucleophilic reactions by the use of nucleophiles such amines, thiols, hydroxyls groups in presence of organic groups with electronic deficiencies showed covalent bonding between heteroatoms (Fig 1a). By this manner, as for example alkoxides could lead to oxidation as well as to nucleophilic reactions depending of the conditions. Thus, by as for example with activated carboxylic groups with the right esters formations or similar could be easily replaced by other nucleophiles with variables secondary chemical structures (Fig. 1b). By this manner, it could be mentioned the carboxylic activation with *N*-Hydroxysuccinimide (Knight, 2001) in aqueous media, the EDC(1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) in intermediate solvent polarities or mixed solvents with a high reactivity for inter-cross linking (Kumar, 2016); and the use of *N*, *N'*-Dicyclohexylcarbodiimide (DCC/DCCD) in apolar solvents (Albert, 2017).

#### a) Nucleophilic Reactions

Amines

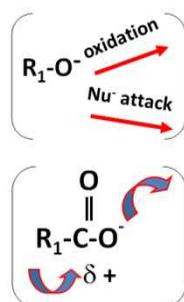
Thiols

Hydroxyls



#### b) Alkoxides

Carboxylate Reactions



**Fig 1.** Scheme of conjugation reaction by covalent bonding: a) by Nucleophilic reactions with varied types of nucleophiles such as Amines, Thiols, Hydroxyl groups; b) further reactions occurred by alkoxides and carboxylic groups.

All the mentioned reagents activated carboxylic groups lowering the Energy of activation of the concerted nucleophilic attack and leaving group in a Substitution Nucleophilic reaction 2 or SN2 (McMurry, 1992).

With just only this example, it could be designed homo-functional, or bi-functional linkers cite formed by variable short molecular spacers cite, and polymeric chains cite that could be chemically modified or inter-crossed with varied reactive agents for targeted reactions involucrated. In this way it could be noted as example; the use of functionalized PEGylated chains; modified hydrocarbons, modified benzene rings, modified lipids, and functional oligomers ( Smith, 2005). In addition to the mentioned nucleophiles it could be used di-thianes (Yus, 2003), di-thiols, thio-amines, etc. In similar manner, other types of strong non-covalent interactions such as adamantane with cyclodextrins macrocycles (Weber and Ohlendorf, 1989) and Biotin-Streptavidin (Chivers, 2011). Interactions could be applied to graft or link chemical structures. Other types of reactions such click chemistry could be developed as well with potential uses in design of new drugs, materials and Nanotechnology (Ha, 2019).

#### Modified Organosilanes

Actually there are many Nanomaterials in current development; where the chemical manipulation from atomic towards higher sized structures is main challenge to afford targeted properties. However, for all the cases were required to achieve covalent and non-covalent bonds by the application of varied chemical reaction types such as the previous ones discussed. In this communication, it was of our interest to communicate some of the most used reactions to design and synthesize Optical Nanoplatforms for multiple applications as Nanotechnology, Biotechnology, Biophotonics and Life Sciences. Therefore, it was developed typical organic chemical reactions between Laser dyes with different functional groups and modified Organosilanes. As it is known, Laser dyes showed to be chemical structures with high Quantum Yields properties that could be affected for their media and close surrounding (Ghazya R, 2004). For this reason, the synthesis and controlled modification of their structures to improve emission efficiencies still being a challenge due to their high sensitivity to media modifications (Hua and Chung, 2016). In addition, their emitter properties could be joined to other ones within

Hybrid Nanomaterials and Metamaterials to design new Nano-emitters and Meta-fluorophores (Woehrstein, 2017) Thus, the use Silica based Nanomaterials provided excellent dielectric properties, optical transparent characteristics that could lead to variable design, study and fabricate devices of variable sizes from the Nano-, to Micro-scale (Soref, 1987). In this way, it should be noted the use of the Störber methodology by sol-gel synthesis for organo-modified silica nanoparticles (Rahman, 2011). However, due to the large application of Silanized materials; motivated to the development of new synthetic methodologies of Nanostructured Silica as well that it should be highlighted (Mcheik, 2018).

In this manner, new Luminescent emitters from the Nano-scale were designed from the molecular control of covalent bonding with the right Laser dyes (Rampazzo, 2017). For example, it was assayed by us the activation of the carboxylic group of Lasers dyes with NHS, EDC, with combination of both; and DCC to react with (3-Aminopropyl) trimethoxysilane (APS) to form fluorescent modified organosilanes (Fig. 2).

So, in controlled conditions it was added to single Organosilane Fluorescent properties. But, it should be mentioned the versatility of these reaction that could be achieved in different condition media depending of the activation agent such aqueous solutions with NHS, intermediate organic polar media for EDC as well as for EDC combined with NHS; and organic solvents with DCC. These were just only few examples that could be applied depending of external conditions required as for Nanotechnology or Life Sciences developments. Moreover, the combinations of reagents as NHS and EDC enhance the activation via the nucleophilic attack of the APS due to a faster kinetics of EDC reaction with the carboxylic group that activate the entrance of the NHS with a global faster and improved nucleophilic substitution of the amine group.

Other example, it was the use of bifunctional modified Laser dyes with Isocyanate groups to react with APS and other types of amined hydrocarbons and other chemical structures adding by this manner varied properties. Moreover the hydroxyls groups could form ester bonds modifying reagents and conditions used when it is need it (Figure 3).

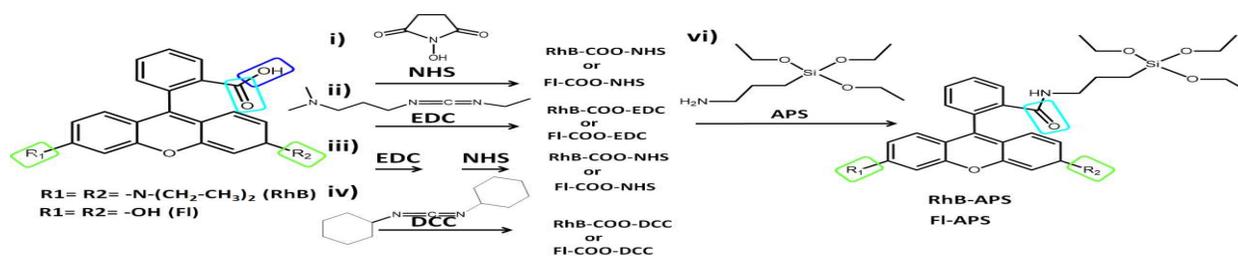
The Isocyanate reactions were achieved in organic solvents; while ester formation in buffer

aqueous solutions to obtain the targeted covalent bonds. In this manner, it could be added a Luminescent Laser dye emitter joined to a hydrolysable Organosilane. So, these types of chemical structures could be polymerized based on concerted SN2 reactions in acid and basic media (Fig. 4a). These reactions could be controlled kinetically and thermodynamically in order to control the stop of the reaction in 2 and 3 dimensions forming films, Nano-, and Micro-structures (Fig 4b). These varied structures are managed modifying organized media, concentrations, pH, etc. Therefore, it was achieved modified surfaces and reduced sized Silica Nanoparticles (Suteewong, 2012 and Ma, 2015).

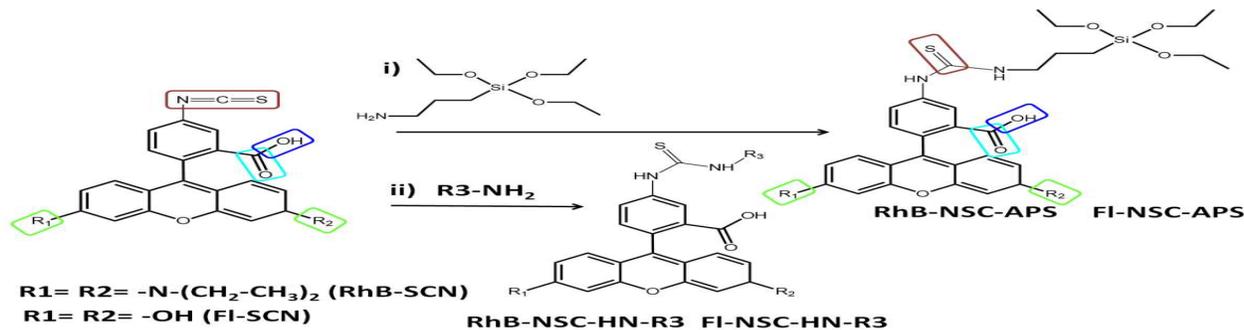
For surface modifications, it could be used different modified Organosilanes such as with amine, isocyanate, hydroxyl, epoxy-, groups that could afford the chemical modification with Laser dyes, Biomolecules, Nanoparticles, Enzymes, Biostructures and further functionalization (Fig 5). It should be noted that the surface could be as for example on deposited metallic films, Nano-surfaces of Nanoparticles and Micro-particles. By this manner, it could be mentioned many developments as for example; patterning self-assembled monolayers with microcontact printing; for new Biosensing methodologies (Mrksich, 1995), Organosilane deposition for microfluidic application (Glass, 2011), Bio-assays for Biostructures and Endotoxins detections (Tinker-Kulberg, 2020); and Smart Molecular responsive surfaces (Siafaka, 2016).

#### *Hybrid Organic and Inorganic Nanocomposites*

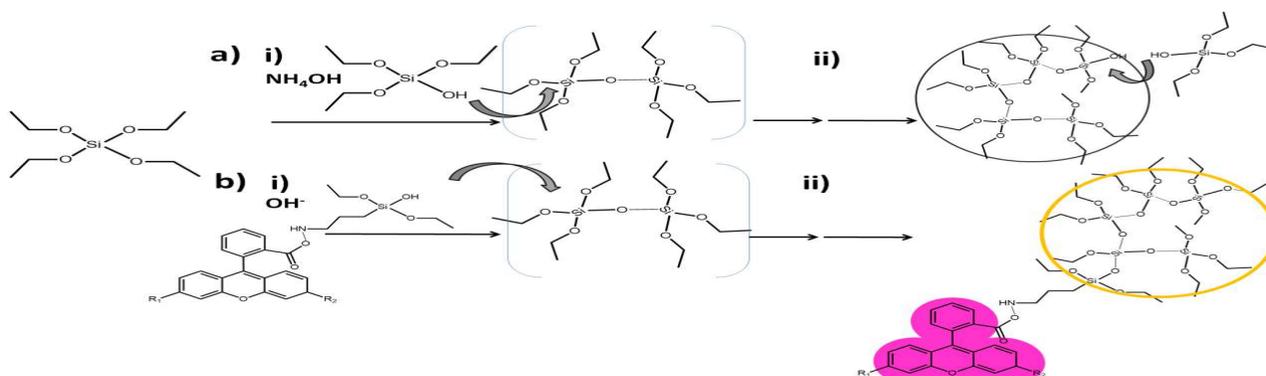
It is of high interest the creation of new Hybrid Nanocomposites joining Organic and Inorganic materials with an accurate control of sizes, lengths molecular positions, within the Nanoscale, below and beyond for the study of new matter properties from their interactions. From literature, Organosilanes with their capability to be modified by different Organic reactions and strategies could afford to target Functionalities. For example based on Bioconjugates technique with the incorporation of organic chemical reactions Silica cargo loaded Nanoparticles for Drug Delivery were reported (Werengowska-Ciećwierz, 2015). But, Silica not only showed the capability of 3D chemical structure formation; as well it permitted the modification of Nano-surfaces within Colloidal dispersion for Bioconjugation and functionalization (Sperling, 2010).



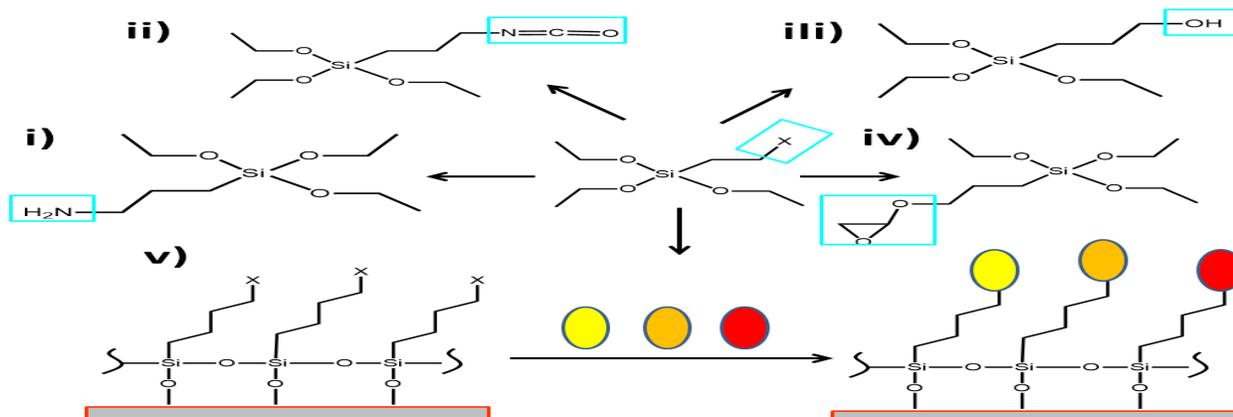
**Fig 2.** Scheme of conjugation reaction of Laser dyes based on Xanthene derivatives by activation of the carboxylic group for nucleophilic reaction with Aminopropyltriethoxysilane (APS).



**Fig 3.** Scheme of conjugation reaction of Laser dyes based on Xanthene by nucleophilic reaction between the Isothiocyanate derivative and Aminopropyltriethoxysilane (APS).



**Fig. 4.** Scheme of hydrolysis reactions of modified Organosilanes: a) Tetraethyl Orthosilicate (TEOS) in basic media; b) TEOS and APS conjugated with Laser dyes.



**Fig. 5.** Scheme of chemical versatility of modified Organosilanes with different organic groups. Modified Tetraethyl Orthosilicate (TEOS) with *i*) amine groups, *ii*) Isothiocyanate group, *iii*) hydroxyls, *iv*) epoxies; and *v*) chemical surface modification by the use of modified Organosilanes and conjugation with other types of molecules such as Optical active structures (represented with coloured ovals).

In this way, it was developed grafted gold Nanoparticles with antibodies for ultrasensitive detection of  $17\beta$ -estradiol (Pinto Oliveira, 2019); the application of click chemistry in nanoparticle modification and its targeted delivery (Yi, 2018); and Maleimide-Based thiolated Nanoparticle to Control Cellular Interactions (Lee, 2020). Moreover, it could be tuned the surface of Nanoparticles with Polyhedral Oligomeric Silsesquioxane Porphyrin Derivatives for targeted Photodynamic Therapy (Siano, 2020). And, it should be highlighted the control of the Nanoscale leading to new structures accompanied with potential functionalities such as porous Silica materials (Hong, 2020) obtained by modifying the media of reaction of the Organosilanes involucrated (Mishra, 2019). Actually, these versatile materials are available on the market with large chemical structure modifications ready to targeted new designs and properties developments. Thus, in the workflow the desired design and study is more accessible.

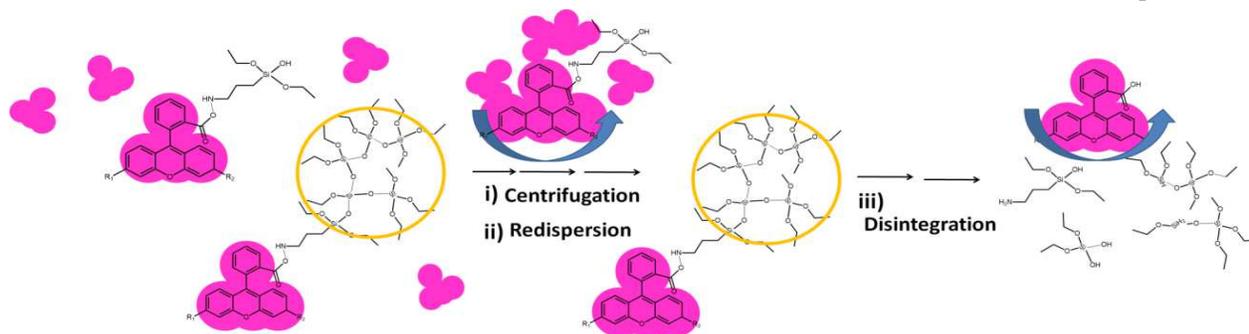
In this way the design and fabrication of Nano-tools such as Lab.-On-particles (Burns, 2006) is of high interest. In this Research field the Nano-Optics should be well developed based on varied material, Metamaterials by the right selection and tuning of Optical active Nanomaterials (Bracamonte, 2020). These optical properties could be joined to Optical active and non-active Biostructures developing by this manner new Nano-Bio-Optics platforms; which could be applied for the detection of Unicellular organisms, Virus towards Higher sized Biostructures, and Single cells (Ame, 2020). For these type of developments the Nano-scale control, composition, and Nano-surface modification, Bioconjugation, and functionalization is required. Therefore, in the different steps of synthesis it should control matter, and molecular compositions. For example, functional organic groups and molecules incorporated within Nanomaterials; such as quantification of amino groups on halloysite surfaces using the Fmoc-method (Fidecka, 2020); and Laser dyes incorporated within tuned silica Nanophotonic platforms based on fluorescence resonance energy transfer (FRET) (Salinas, 2020).

In these Nanoplatforms were incorporated variable Laser dyes in order to tune non-classical light emissions based on FRET. For these Nano-emitters was quantified the Laser dyes

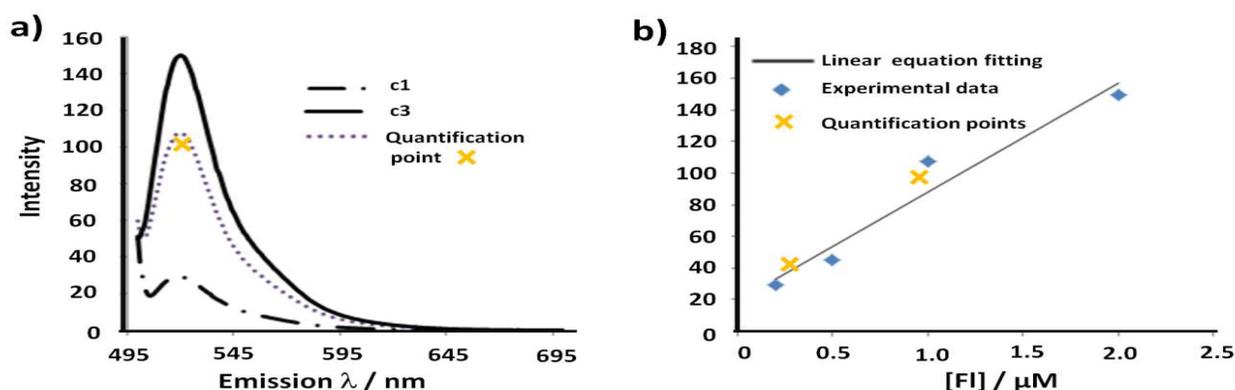
incorporation within a large varied concentrations from Nano-Molar to Micro-Molar interval. Different ways of emitter quantifications should be applied accurately in order to optimize emissions from single emitters to controlled inter-molecular dyes. For the quantification should be considered in the different steps of reactions, centrifugations and re-dispersions for cleaning (Fig. 6).

Thus, free dyes could be collected; and from the difference between the total concentrations added and unreacted free conjugated dyes were quantified. In this manner, as for example by Static Fluorescence could be prepared Calibration curves for the quantifications (Fig. 7). From the control of added Lasers dyes Enhanced Luminescent Nanoplatforms based on FRET for targeted non-classical light delivery applications were developed (Salinas, 2020).

The Luminescence emissions recorded from Single Nanoplatforms by Laser Fluorescence Microscopy, showed proportional intensities and variable wavelength intervals depending of concentrations added, related Quantum Yields, and activation of FRET phenomena. The Silica Nanoparticles obtained were well dispersible in Colloidal dispersion, and well spherical shapes defined (Fig. 8a). The Mono-coloured Silica Nanoplatforms with Rhodamine B (RhB) showed well defined Luminescent Nanoparticles (Figure 8.b); but by the use of Fluorescein (Fl) was augmented the emission intensity due to its higher Quantum Yield (Fig. 8c and 8d). However, by the addition of both Laser dyes Enhanced emissions non-explained by the sum of both individual contributions were collected (Fig 8e and 8f). Thus, it was controlled the non-classical emissions from well-defined Luminescent Nanoparticles towards higher emissions that generated bigger diameters accompanied with diminished photobleaching properties. Then, these Silica Nanoplatforms showed tide interactions with Bio-membranes such as Optical active Unicellular organisms based on non-covalent interactions. In this point it is important to note that polar interactions, hydrogen bridges; and additional interaction with particular Biomolecules of membranes are involucrated (Gammoudi, 2013). Therefore, sizes of Nanoparticles, chemical modification of Nanosurfaces and membranes compositions showed varied resolutions by Laser Fluorescence Microscopy. In addition, it should be contemplated additional non-classical light



**Fig. 6.** Scheme of hydrolysis and polymerization of modified conjugated Tetraethyl Orthosilicate (TEOS) with Aminopropyltriethoxysilane (APS) linked to Laser dyes, to form Luminescent Nanoarchitectures. Step i) centrifugation, ii) re-dispersion of the Nanoarchitectures obtained and collection of the supernatant with non-reactive APS-Laser dye, iii) disintegration of the Nanoarchitecture and collection of the incorporated APS-Laser dye by covalent linking.



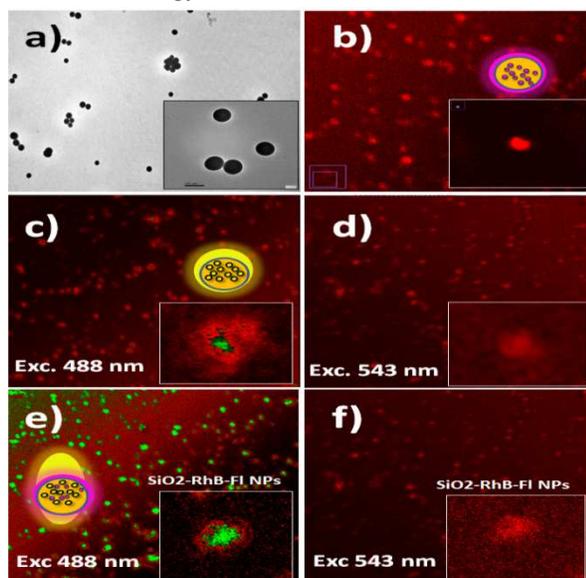
**Fig 7.** Quantification of APS-Laser dye incorporated within the Nanoarchitecture of Luminescent Nanoparticles: a) Fluorescence emissions of two calibration curve points made, and from the sample collected from the supernatant after conjugation; b) Representative calibration curve with quantification points at different levels of concentrations with highlighted yellow cross.

pathways and coupling phenomena depending of the Optical activity of the Biostructure and Nanoemitters used. By this manner, it was showed by us the targeted delivery of Synthetic non-classical luminescence by Enhanced Silica Nanophotonics on Cyanobacteria. Thus, it was generated Higher augmentations of Nano-Bio-luminescence based on Nano-Bio-FRET (Salinas, 2020) pathways. These additional increases were recorded by controlling the light delivered on targeted natural photo systems known as PS I and PS II. of Cyanobacteria (Yamazaki, 1984). Just to mention; the mentioned phenomena in volucrated are related with high impact Research related with Living Lasers (Meech, 2011), Biolasers (Gather, 2011), and new Laser Nano-Biostructures (Salinas, 2020); as well as for the development of new strategies of Single Molecule Detection (SMD) (Nie, 1994 and Veglia, 2019).

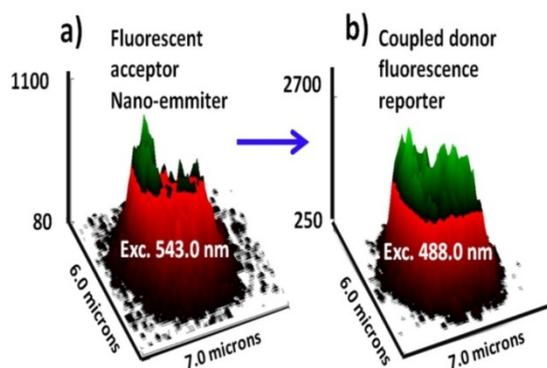
In addition, these Optical active Enhanced Luminescent Nanoplatforms were evaluated for design of Smart Opto-responsive substrates. In

this way, the Multi-coloured Nano-emitters were deposited on modified silanized cover glass slides. The multi-deposition of the Nanoparticles controlling their colloidal dispersion concentrations permitted the controlled Multi-layered Nanoparticle depositions. In optimal conditions, it was possible to activate varied emissions by switching the Laser excitation wavelength; such as from 543.0 nm to optimally excite just only the Fluorescence Energy acceptor (Fig. 9a); while by 488.0 nm excitation the Fluorescence Energy donor (Fig. 9b). Thus, it was showed the coupled FRET pathways that generated substrates with improved materials properties such as; i) higher emission intensities; ii) larger Ultraluminescent surfaces; iii) wider transmission of non-classical light across the modified substrate within the micrometer scale; and iv) absence of photobleaching properties. It should be noted that these Nanostructured surfaces could afford to further chemical modifications for functionalization and 3D hierarchical bottoms up fabrications (Kumar, 2017).

So, it was showed how from the molecular covalent bonding with functional building blocks as Organosilanes could be designed versatile Nanoplatforms with potential implications in Nanotechnology and Functional devices.



**Fig 8.** Nanoimaging of Luminescent Nanoparticles based on conjugated Tetraethyl Orthosilicate (TEOS) with Aminopropyltriethoxysilane (APS) linked to varied Laser dyes: a) representative TEM image of Nanoparticles obtained. Inset image corresponded to 250 nm Nanoparticle diameters; b) Laser Fluorescence Microscopy (LFM) of Mono-coloured Nanoparticles by incorporation of Rhodamine B (RhB) as Laser dye. Laser excitation at 543.0 nm; c) and d) LFM of Mono-coloured Nanoparticles by incorporation of Fluorescein (FI). Laser excitation at 488.0 nm and 543.0 nm respectively; e) and f) LFM of Multi-coloured Nanoparticles by incorporation of RhB and FI as Fluorescence Energy Transfer (FRET) pairs. Laser excitation at 488.0 nm and 543.0 nm respectively.



**Fig 9.** 3D fluorescence surfaces from deposited multi-colored nanoparticles on silica substrates: a) with only optimal excitation of Rh Basafluorescent energy acceptor at 543 nm and b) only optimal excitation of Flasa fluorescent energy donor at 488 nm and coupling with RhB as a fluorescent energy acceptor via FRET.

## Conclusion

In this communication it was introduced some of the most used organic chemical reactions for covalent bonding of different fundamental molecular building blocks. Thus, controlled properties were generated by joining Laser Fluorescent dyes and polymerizable modified Organosilanes. In this context, it was discussed the applications of classical conjugations and Bioconjugations reactions based organic chemistry using variable solvents and chemical reagents that afforded to develop covalent bonding in different media depending of needs. Moreover, it was showed and discussed the versatility of the modified Organosilanes for different types of reactions. Therefore, it was permitted the modification of larger surface and substrate modifications, as well as to Nano-surfaces applications.

In addition, the chemical precursors obtained permitted the synthesis and design of controlled Luminescence emissions from Silica Nanoplatforms. In this manner it was developed Enhanced Luminescence based on FRET, and Bio-FRET controlling the Energy transference by Laser excitation.

Finally, it should be mentioned that further potential uses and applications could be developed by joining their molecular building block properties on varied Nano-matter composition and patterned surfaces to design new Opto-active Nanoplatforms and Organized systems. By this manner it could be mentioned Light responsive DNA detection (Brouard, 2011) by coupling FRET signaling with Metal Enhanced Fluorescence (MEF) (Brouard, 2013) based on modified silver Cores templates. Moreover, these strategies could be extended to hybrid Organic/Inorganic organized systems by FRET signaling (Gruber, 2010) as well for the detection of peptides related with thrombin and blood coagulation (Muller, 2014). So, there is high potential for the design of versatile and Functional surfaces and Nanoplatforms.

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