Synthesis, Characterization and Theoretical Studies of new Azo compound derived from Coumarin

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الخلاصة

تم تحضير مشتق كومارين جديد N'-(3-bromobenzylidene)-4-((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diazenyl)benzohydrazide و تم تشخيصه بالاشعة فوق البنفسجية ، و الاشعة تحت الحمراء و اطياف الرنين النووي المغناطيسي ثم دراسة استقرارية المركب المحضر باستخدام نظرية دالة الكثافة .

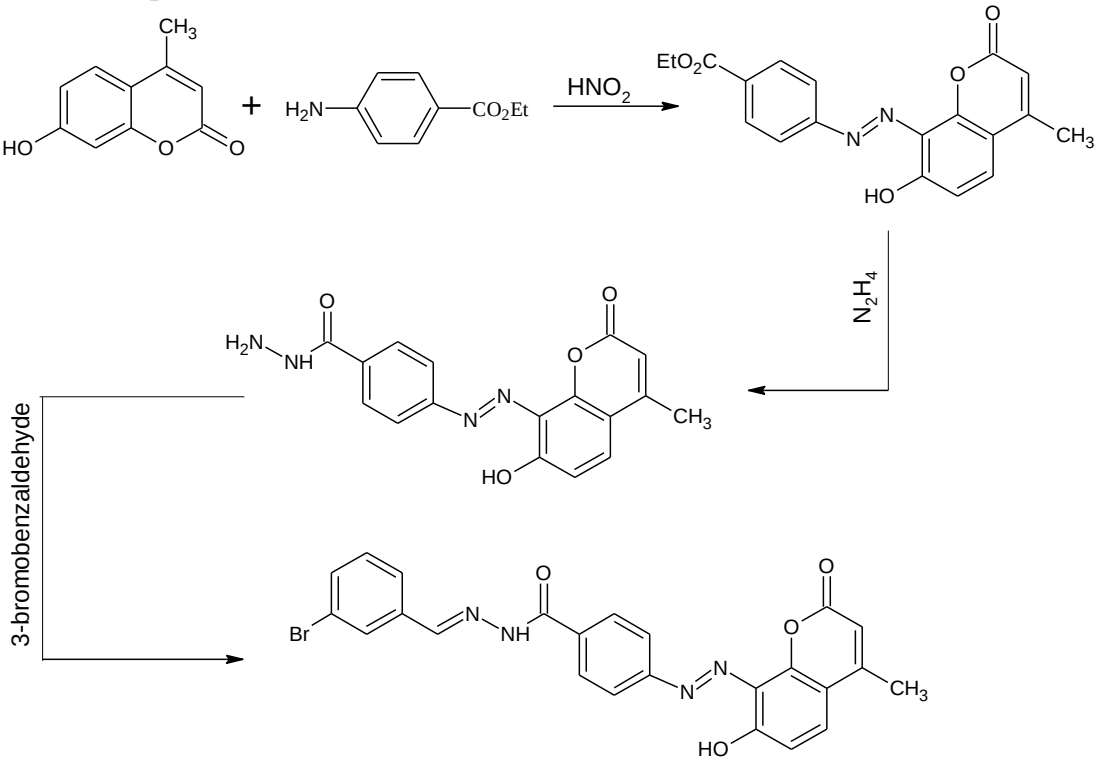
ABSTRACT

New coumarin derivatives, namely, N'-(3-bromobenzylidene)-4-((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diazenyl)benzohydrazide was synthesized and characterized by means of it UV-VIS, FT-IR and ^{1}HNMR spectral data. Density Functional Theory (DFT) calculations for the synthesized compound was performed using molecular structure with optimized geometry. Molecular orbital calculations have provided detailed descriptions of the orbitals, including spatial characteristics, modal patterns, and the contributions of individual atoms.
Keywords: Coumarin; DFT; diazo; HOMO; LUMO

INTRODUCTION

Coumarins have drawn considerable attention from researchers due to their role in natural and synthetic organic chemistry, and their interesting biological activities. Compounds which contain a coumarin nucleus were found to exhibit various biological activities such as anticoagulant and antithrombotic properties [1]. Some derivatives have shown molluscicidal, anthelmintic [2], hypnotic, and insecticidal [3] activity, while others have served as antifungal [4], anti-inflammatory [5] and antiviral agents, including against human immunodeficiency virus [6], and anticoagulant properties [7]. In addition, coumarins have also been used as additives in food and cosmetics [8], and in the preparation of optical brighteners, dispersed fluorescent and laser dyes [9]. On the other hand, the nitrogen and sulfur heterocyclic system families are very interesting due to their physicochemical properties, especially in the sense of design of new drugs and new materials. The chemistry and pharmacology of thiazole derivatives has been of great interest to medicinal chemists lately [10]. The pyrazole ring is a prominent structural moiety found in numerous pharmacologically active compounds. Pyrazole-based derivatives have been regarded as anxiolytics [11], gamma-amino butyric acid (GABA) receptor antagonists and insecticides [12], Positron emission tomography (PET) ligands for cannabinoid receptor type 1 (CB1) receptors [13], anti-inflammatory, antimicrobial [14], and growth inhibition agents [15].

Based on these findings, we try to describe the synthesis and characterize of new compound featuring different heterocyclic rings fused onto the coumarin, with the aim of obtaining more potent pharmacologically active compound. (Scheme1).



Scheme1. Reaction sequences of the synthesis of N'-(3-bromobenzylidene)-4-((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diazenyl)benzohydrazide.

MATERIALS AND METHODS

General

The chemicals used during synthesis were supplied by Sigma-Aldrich. Purity of the compounds was
checked on thin layer chromatography (TLC) plates (Silica gel G). The spots were located under 365 nm UV light. Infrared spectra were recorded as KBr discs using a SHIMADZU FT-IR 8400S spectrophotometer, at the Chemistry Department, Al-Mustansyriyah University. The Proton NMR spectra (solvent DMSO-d_6) were recorded on Bruker DMX-500 spectrophotometer -300 MHz spectrometer with TMS as internal standard which were made at chemistry department , Al-Bayt University, Jordan. A Gallenkamp M.F.B.600.010 F melting point apparatus was used to measure the melting points of all the prepared compounds.

Synthesis of 7-hydroxy-4-methylcoumarin

A mixture of the resorcinol (30 mmol), ethyl acetoacetate (30 mmol) and sulfuric acid was heated at 100-120 °C for 3 hrs. After cooling to room temperature, the mixture was poured into 50 g of crushed ice. The crystals

formed were filtered off, washed with water and air dried to give crude, the products recrystallized from the ehanol to give 7-hydroxy-4-methylcoumarin.

Synthesis of ethyl 4-[(E)-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diazenyl]benzoate

4-amino ethyl benzoate (0.01 moles) is added to a solution of water (4 ml) and concentrated hydrochloric acid (2.25 ml). The resulting solution is stirred for 10 min., before being cold to (0-5) C°. A solution of sodium nitrite (0.011 moles, 0.76 gm) in water (2.5 ml) is added drop wise. After being stirred for 10 min., the resulting solution of diazonium salt was added drop wise to mixture of 7-hydroxy-4-methylcoumarin (1.7620g, 0.01 mole) in ethanol and 10% NaOH (10 ml) at (0C° -5C°) and PH=5.5. After the addition was completed, the mixture was stirred for further 20 min. than was left for 1 hour, the resulting solid was filtered and washed with water, dried and recrystallized from ethanol.

Synthesis of 4-[(E)-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diazenyl]benzohydrazide

To a solution of ethyl 4-[(E)-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diazenyl]benzoate

(0.06 mole, 9.9114 g) in (25ml) of ethanol, hydrazine hydrate (80%) (0.0 moles, 30 ml) was added drop wise with stirring. The mixture was refluxed for (12 hour), cooled then solid formed was filtered and recrystallized from ethanol: water (1:1).

Synthesis of N'-(3-bromobenzylidene)-4-((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diazenyl)benzohydrazide

To a solution of 4-[(E)-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diazenyl]benzohydrazide (0.354gm., 0.001 mole) in (20 ml) of absolute ethanol, 3-bromobenzaldehyde (0.001 moles) was added with 3-4 drops of glacial acetic acid. The mixture was refluxed for (6-8) hours, reaction mixture was cooled then the solid formed was filtered and recrystallized from ethanol.

Theoretical Studies

The molecular representation sketch of the reference compound was plotted using ChemBioOffice 2010 software. All the quantum chemical calculations were performed using the Density Functional Theory (DFT) methodology with 3–21G basis set, while the molecular atomic charges were calculated via the Mulliken population analysis.

RESULTS AND DISCUSSION

For the synthesis of target compound N'-(3-bromobenzylidene)-4-((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diazenyl)benzohydrazide,

the reaction sequence is outlined in Scheme 1, started from 7-hydroxy-4-methylcoumarin, that can be synthesized via Pechmann reaction by the refluxing of resorcinol and ethyl acetoacetate in the presence of concentrated sulfuric acid. As described in the literature [16, 17], the Pechmann reaction was carried out with toluene as a solvent. The use of other aromatic and nonaromatic solvents with other boiling points did not improve the yield of the desired (oxo-2H-chromen-8-yl)diazenyl]benzohydrazide and 3-Bromo benzaldehyde. The FT-IR spectrum of target compound showed absorption bands in the 3410 and 3471 cm^{-1} (-NH), 1678 cm^{-1} (-C=O carbonyl stretching), and 1624 cm^{-1} (N=C stretching), and 1562 cm^{-1}(N=N stretching). The ^{1}H-NMR spectrum(300 MHz; DMSO-d6) δ2.65(s,3H), 5.35(m,1H), 6.23(s,1H), 7.11-7.87(m,2H), 8.05-8.20(m,4H), 8.40(s,1H), 7.42-7.85(m,4H)ppm.

Computational Studies

Mulliken Charges and Stabilities

The theoretical studies [18-20] had shown that the atomic charges were affected by the presence of the substituent of the rings. The minimized geometry is shown in Figure 1, where the calculated atomic charges for the new coumarin are also indicated, Table 1. Highest atomic charge is at [O (8) −0.3570)] and the next charge values are at [O (23) −0.3176] and [C (18) −0. 2410]. These results clearly indicated that these three atoms are the most reactive sites toward the reactions and bonding with the metals. The calculated bond and twist angles and 3D-geometrical structure, indicated that this molecule is not planar moreover the stereochemistry is N (10)-C (26): (E), N (11)-N (12): (Z) .(8) is 1.2210.

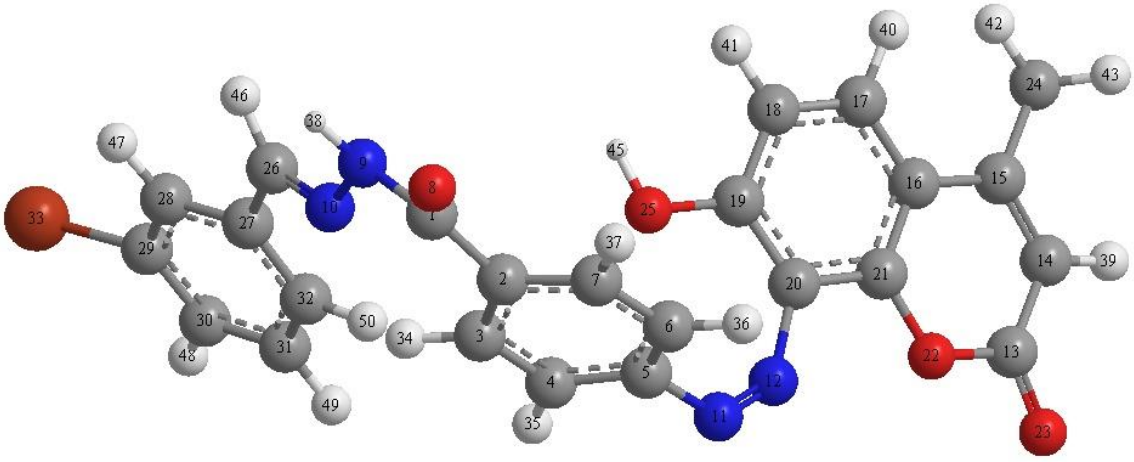


Figure 1. 3D-geometrical structures for new coumarin

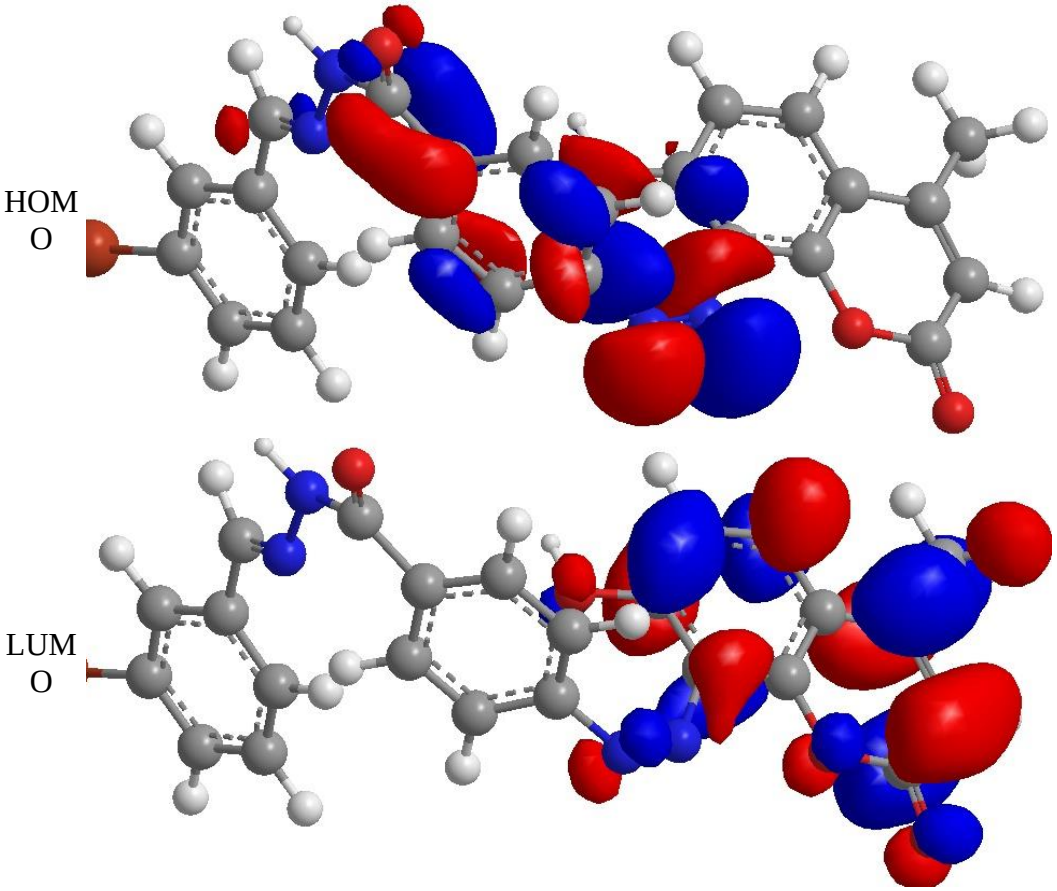
Table 1: The Mulliken Charges of new synthesized coumarin

Atoms	Mulliken Charges	Atoms	Mulliken Charges	Atoms	Mulliken Charges
C(1)	0.3236	C(17)	0.0158	Br(33)	0.0067
C(2)	-0.1298	C(18	-0.2410	H(34)	0.1462
C(3)	-0.0693	C(19)	0.1641	H(35)	0.1193
C(4)	-0.1036	C(20	-0.2016	H(36)	0.1176
C(5)	-0.0560	C(21)	0.2012	H(37)	0.1208
C(6)	-0.1194	O(22)	-0.1336	H(38)	0.0844
C(7)	-0.0397	O(23)	-0.3176	H(39)	0.1407
O(8)	-0.3570	C(24)	-0.0910	H(40)	0.1159
N(9)	-0.0113	O(25)	-0.2212	H(41)	0.1228
N(10)	-0.1108	C(26)	-0.0722	H(42)	0.0552
N(11)	0.0242	C(27)	-0.0630	H(43)	0.0619
N(12)	0.0701	C(28)	-0.0673	H(44)	0.0620
C(13)	0.3884	C(29)	-0.1168	H(45)	0.2135
C(14)	-0.2335	C(30)	-0.0696	H(46)	0.1086
C(15)	0.0472	C(31)	-0.0984	H(47)	0.1235
C(16)	-0.1982	C(32)	-0.0763	H(48)	0.1244

Density Function Theory (DFT)

DFT calculations were performed for new coumarin. The optimized molecular structures of the most stable forms are shown in Figure 1. Molecular orbital calculations provide a detailed description of orbitals including spatial characteristics, nodal patterns and individual atom contributions[21]. The contour plots of the frontier orbitals for the ground state of new coumarin are shown in Figure 2, including the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO)[22]. It is interesting to see that both orbitals are substantially distributed over the conjugation plane. It can be seen from Figure 2 that the HOMO orbitals are located on the substituted molecule while LUMO orbitals resemble those obtained for the unsubstituted molecule and therefore the substitution has an influence on the electron donation ability, but only a small impact on electron acceptance ability. The orbital energy levels of HOMO and LUMO of new coumarin are (-5.168) and (-4.035) eV respectively, and the Heat of Formation is (31.896) Kcal/Mol. It can be seen that the energy gaps between HOMO and LUMO is about (1.133) eV. for new coumarin, and the lower value in the HOMO and LUMO energy gap explain the eventual charge transfer interaction taking place within the molecules[23].

Table 1. HOMO and LUMO energies of new coumarin



CONCLUSIONS

In this study, the new coumarin has been synthesized and characterized using various spectroscopic methods UV-VIS, FT-IR and ^{1}HNMR and elemental analysis technique. The synthesized compound was studied theoretically and it atomic charges and stereochemistry were estimated and it was found it is not planar.

REFERENCES

[1] Murray, R.D.H.; Mendenz, J.; Bouwn, S.A. *The Natural Coumarins*; Wiley & Sons: New York, NY, USA,(1982).

[2] Schonberg, A.; Latif, N. Furochromones and coumarins. XI. The molluscicidal activity of bergapten, isopimpinellin, and xanthotoxin. *J. Am. Chem. Soc.*, *76*, 6208, (1954).

[3] Mitra, A.K.; Misra, S.K.; Patra, A. New synthesis of 3-alkyl coumarins. *Synth. Commun.*, *10*, 915-919,(1980).

[4] Sardari, S.; Mori, Y.; Horita, K.; Micetich, R.G.; Nishibe, S.; Daneshtalab, M. Synthesis and antifungal activity of coumarins and angular furanocoumarins. *Bioorg. Med. Chem.*, *7*, 1933-1940, (*1999*).

[5] Khan, M.S.Y.; Sharma, P. Synthesis of new α-pyronoflavones and related products. Part II. *Indian J. Chem. ,32*, 817-821,(1993).

[6] Xie, L.; Takeuchi, Y.; Cosentino, L.M.; MacPhail, A.T.; Lee, H.K. Anti-AIDS agents. 42. Synthesis and anti-HIV activity of disubstituted (3'R, 4'R)-3', 4'-di-O-(S)-camphanoyl-(+)-ciskhellactone analogues. *J. Med. Chem.*, *44*, 664-671, (2001).

[7] Singer, L.A.; Kong, N.P. Vinyl radicals. Stereoselectivity in hydrogen atom transfer to equilibrated isomeric vinyl radicals. *J. Am. Chem. Soc*., *88*, 5213-5219, (1966).

[8] O'Kennedy, R.; Thornes, R.D. *Coumarins: Biology, Application and Mode of Action*; Wiley & Sons: Chichester, UK,(1997).

[9] Zahradnik, M. *The Production and Application of Florescent Brightening Agents*; Wiley & Sons: New York, NY, USA, (1992).

[10] Nora de Souza, M.V. Synthesis and biological activity of natural thiazoles: An important class of heterocyclic compounds. *J. Sulfur Chem.*, *26*, 429–449, (2005).

[11] Geronikaki, A.; Babaev, E.; Dearden, J.; Dehaen, W.; Filimonov, D.; Galaeva, I.; Krajneva, V.; Lagunin, A.; Macaev, F.; Molodavkin, G.; Poroikov, V.; Pogrebnoi, S.; Saloutin, V.; Stepanchikova, A.; Stingaci, E.; Tkach, N.; Vladg, L.; Voronina, T. Design, synthesis, computational and biological evaluation of new anxiolytics. *Bioorg. Med. Chem.*, *12*, 6559–6568,(2004).

[12] Sammelson, R.E.; Caboni, P.; Durkin, K.A.; Casida J.E. GABA receptor antagonists and insecticides: common structural features of 4-alkyl-1-phenylpyrazoles and 4-alkyl-1-phenyltrioxabicyclooctanes. *Bioorg. Med. Chem.*, *12*, 3345–3355, (2004).

[13] Kumar, J.S.; Prabhakaran, J.; Arango, V.; Parsey, R.V.; Underwood, M.D.; Simpson, N.R.; Kassir, S.A.; Majo, V.J.; Van Heertum, R.L.; Mann, J.J. Synthesis of [*O*-methyl-11C]1-(2- chlorophenyl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide: a potential PET ligand for CB1 receptors. *Bioorg. Med. Chem. Lett.*, *14*, 2393–2396, (2004).

[14] Bekhit, A.; Abdel-Aziem, T. Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents. Bioorg. Med. Chem., 12, 1935–1945,(2004).

[15] Baraldi, P.; Beria, I.; Cozzi, P.; Bianchi, N.; Gambari, R.; Romagnoli, R. Synthesis and growth inhibition activity of α-Bromoacrylic heterocyclic and benzoheterocyclic derivatives of distamycin A modified on the amidino moiety. Bioorg. Med. Chem., 11, 965–975,(2003).

[16] M.C. Laufer, H. Hausmann, and W.F. Hölderich Synthesis of 7-hydroxycoumarins by Pechmann reaction using Nafion resin/silica

nanocomposites as catalysts Journal of Catalysis 218 , 315–320,(2003).

[17] Hakan Kolancilar Investigation of Pechmann condensation products of ethyl acetoacetate with 2,7-dihydroxynaphthalene Trakya Üniversitesi Bilimsel Araştırmalar Dergisi B Serisi, Cilt 3, No 1, 7-10,(2002).

[18] Al-Amiery, A.A.; Al-Majedy, Y.; Abdulreazak, H.; Abood, H. Synthesis, Characterization, Theoretical Crystal Structure, and Antibacterial Activities of Some Transition Metal Complexes of the Thiosemicarbazone. Bioinorg. Chem. Appl., 2011, 1–5,(2011).

[19] Kadhum, A.A.H.; Mohamad, A.; Al-Amiery, A.A. Antimicrobial and anti-oxidant activities of new metal complexes derived from 3-aminocoumarin. Molecules, 16, 6969–6984,(2011).

[20] Al-Amiery, A.A.; Al-Bayati, R.; Saour, K.; Radi, M. Cytotoxicity, Antioxidant and Antimicrobial activities of novel 2-quinolone derivatives derived from coumarins. Res. Chem. Intermediat , 38, 559–569,(2012)..

[21] Al-Amiery, A.A.; Musa, A.Y.; Kadhum, A.A.H.; Mohamad, A. The use of umbelliferone in the synthesis of new heterocyclic compounds. Molecules, 16, 6833–6843,(2011).

[22] Al-Amiery, A.A.; Musa, A.Y.; Kadhum, A.A.H.; Mohamad, A. The Antioxidant Activity of New Coumarin Derivatives. Int. J. Mol. Sci., 12, 5757–5761, (2011).

[23] Kadhum, A.A.H.; Al-Amiery, A.A.; Shikara, M.; Mohamad, A.; Al-Bayati, R. Synthesis, Structure elucidation and DFT studies of New thiadiazoles. Int. J. Phys. Sci., 6, 6692–6697, (2012).