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Synthesis, Characterization of Isoindolinones and their Molecular Docking, Photochemical Studies

D. Sivasankaran*[1] and A. Mangalam[2]

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A B S T R A C T

Novel series of isoindolinone derivatives (4a-g) have synthesized and characterized by ^{1}H-NMR, ^{13}C-NMR, Mass and elemental analysis. In-silico molecular docking studies exhibited that synthesized compounds 4a and 4g are good binding energy (-8.46kcal and -9.46kcal) towards the essential requirements of targeted compounds for EGFR receptor-bearing isoindolinone inhibitor (PDB ID: 1M17(Lapitinib)). UV-Vis and fluorescence spectroscopy measurements provided a significant effect on the absorption, emission cyclic voltammetry (CV) and HOMO, LUMO values of compound 4g are also confirmed band along with intramolecular charge transfer character (D-π-A). The red shift maxima (510 nm) the emission spectra in various solvents with increasing solvent polarity.

***Key words*:** Isoindolinones, Molecular docking, EGFR-inhibitors, Photochemical study, DFT

Isoindolinones are N-hetero-cyclic scaffolds comprise the key structural feature of a wide range of synthetically and biologically active molecules. 3-Alkyl-2,3-dihydro-1H-isoindolin-1-ones 1a−d manifest activities such as antihypertensive [1], antipsychotic [2], anti-inflammatory [3], anesthetic [4], antiulcer [5], vasodilatory [6], antiviral [7], antileukemic [8] and are also used in the synthesis of various drugs [9]. Few members of isoindolinones are known to have platelet aggregation inhibitory activity [10], and are shown to induce dose-dependent p53-dependent gene transcription in MDM2-amplified SJSA human sarcoma cell lines [11].

MATERIALS AND METHODS

All the solvents and chemicals were used analytical grade from sigma Aldrich and Merck Ltd. TLC was performed on commercial Merck silica gel 60 F 254. Column chromatography was carried out using silica gel 60-120 mesh. ^{1}HNMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using TMS an internal standard with Bruker 400MHz NMR spectrometer. ESI mass was recorded using a Thermo Fleet-LC mass instrument.

General Synthetic procedure for isoindolinone derivatives (4a-h)

A solution of an aldehyde (0.3 mmol), an amine (0.3 mmol) and Zn(OTf)2 in dry chloroform was stirred at ambient temperature for 15-30 min in a closed vessel. Allyltributylstannane (0.45) was added and the whole reaction mixture was stirred at 35°C temperature until completion (monitored by TLC). The reaction mixture was concentrated *in vacuo* and purified over silica gel by column chromatography (20-60% EtOAc in hexanes) affording products in up to 93% yields.

RESULTS AND DISCUSSION

The synthesis route for the novel (4a-h) isoindolinone derivatives is illustrated in Scheme 1. The isoindolinones were synthesized from one-pot three-component allylation of imine followed by lactamization sequence using methyl o-formyl benzoate 1a, substituted aniline 2 in the presence of 10 mol % of $Zn(OTf)_2$ as a catalyst in dry chloroform was stirred at ambient temperature for 15-30 min in a closed vessel. Allyltributylstannane (0.45) was added and the whole reaction mixture was stirred at 35°C temperature until completion (monitored by TLC). The reaction mixture was concentrated in vacuo and purified over silica gel by column chromatography (20-60% EtOAc in hexanes) afforded expected isoindolinones 4a-h in up to 93% yields.

The ^{1}H-NMR spectrum of compound 5a was confirmed by the presence of multiple signals at 5.26-5.3 ppm, 5.22 ppm, 4.92 ppm assigned to protons from allyl group and the doublet signal 2.52-2.70 shows alkyl proton of isoindoline ring and adjacent methyl group and another multiple signal 7.38-7.40 represent aromatic group proton of isoindolinone and aryl grops. [13] C NMR spectra the characteristics carbonyl carbon of amide group appeared at 167.2 ppm. The ethylene carbon signal appeared in the range of 122.4, 119.7 ppm. The other signals 144.1, 135.4, 134.3, 132.4, 131.9, 130.7, 128.5, 127.6,

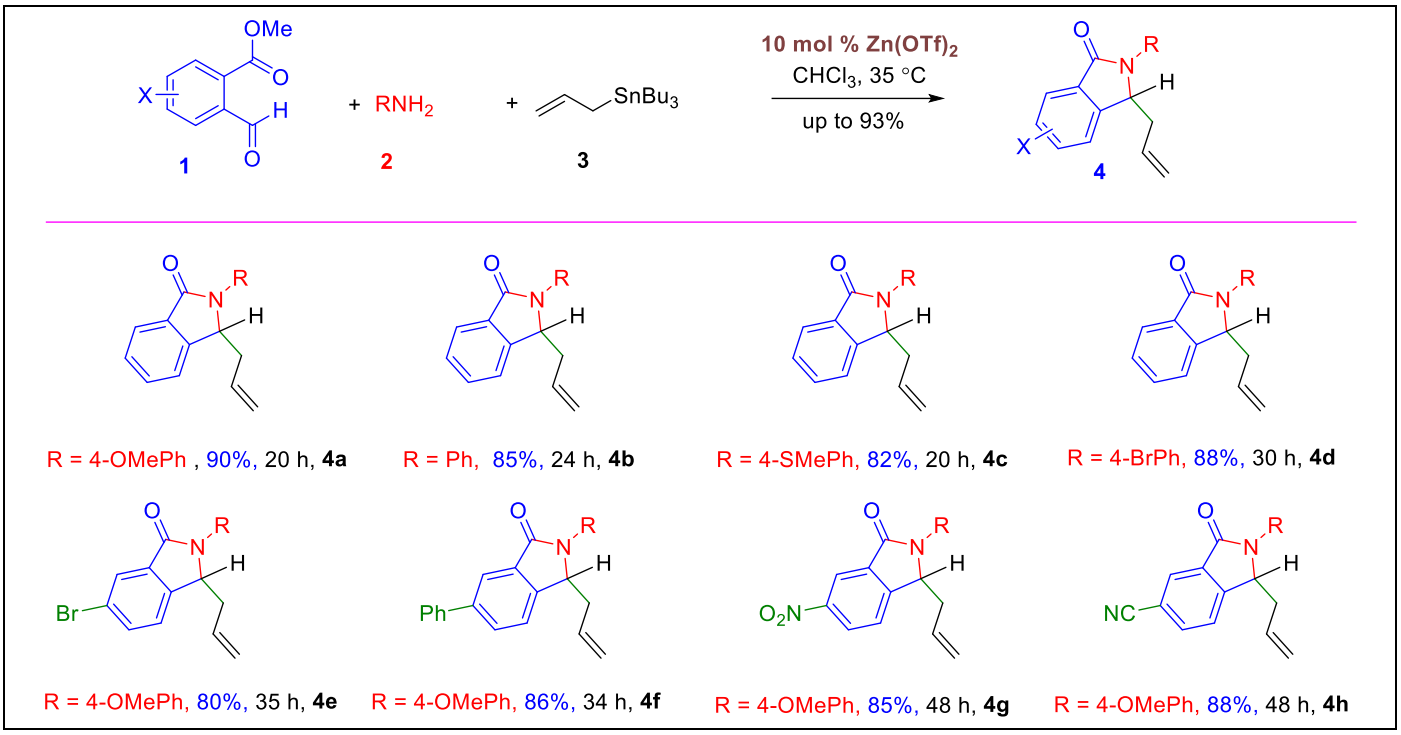
* **D. Sivasankaran**
✉ sivasankaran.chem@bharathuniv.ac.in

[1-2] Department of Chemistry, Bharath Institute of Higher Education and Research (BIHER), Chennai - 600 073, Tamil Nadu, India

124.1 ppm corresponds to the aromatic region accounts for the aryl carbon. The NMR spectra showed the formation of target compounds 5a.

Molecular docking

In order to design our targeted compounds, the essential requirements for EGFR receptor bearing isoindolinone inhibitor (HDAC6) were studied (Fig 2). It was found that a hydrogen bond acceptor of quinazoline ring interacts with Met769 [28]. The crystal structure of epidermal growth factor receptor with erlotinib (Tarceva™) (PDB code: HDAC6) [29-30].



Scheme 1 Synthesis of isoindolinone derivatives (4a-h)

The docking of synthesized compounds with receptor RTK exhibited well-established bonds with one or more amino acids in the receptor active pocket. The compounds 4a, 4e, 4f and 4g show very high binding energy with the RTK (1m17) receptor in (Fig 2). The compound 4a exhibits binding energy value -8.46 kcal/mol showed three H-bonding, the ligand of carbonyl group bonded with Lys721 (1.67Å) and OCH_3 bonded with amino acid residue of Met769 (2.26Å), Pro770 (2.44 Å) as well as aromatic region exhibit the strong affinity of Arg817, Val702, Lys721, Leu764 which results from four hydrophobic interaction with RTK receptor in (Fig 2a). The compound 5e also exhibits strong binding energy -8.64kcal/mol which result five H-bonding, the substituted hydroxyl group bonded with Glu738 (2.56 Å) and amide of nitrogen bonded with Asp891 (2.28 Å), carbonyl group interact Arg817 (3.37 Å), nitrogen bonding with Arg817 (2.95 Å) in (Fig 2b). The binding energy of compounds 4g and 4f are -8.24 kcal/mol and -9.46, respectively. The compound 5g had hydrogen bond donor interaction with Leu768(2.15Å), hydrogen bond acceptor interaction with Met769 (1.84 Å), It has been observed to be hydrophobically enclosed with active site amino acid residues Ala719, Leu694, Try777, Leu820, His781, Phe771 (Fig 2c)). The compound 4f had two hydrogen bond acceptor with Leu768 (2.19 Å) and one hydrogen bond donor interaction with Met769 (1.98Å), one hydrogen bond acceptor interaction with Glu780 (2.19Å), It has also depicted hydrophobic enclosure with the active site amino acid residues Al719, Leu694, Leu820, Phe771, Glu772 (Fig 2d). (2.06 Å). Our prior studies showed important interacting residues of known EGFR inhibitors were MET-793. *In-silico* molecular docking studies revealed all the synthesized molecules showed good binding energy towards the target receptor RTK. Generally, the functional groups (amine and ketone) are forming the hydrogen bond with amino acid residues (Fig 2). The free energy of binding (FEB) of all compounds was calculated.

Photochemical studies

The absorption and emission spectra of compound 4g recorded in various solvents like nonpolar, polar aprotic and were protic solvents studied are shown in (Fig 3a, b) and the corresponding spectroscopic, optical band gap and photophysical properties are collected in (Table 2). The emission band is found to shift towards longer wavelengths with increasing solvent polarity due to the stabilization of the charge-transfer transition in polar solvents. The observed higher value of the Stokes shift on moving from non-polar to polar solvents, this was indicated that the intramolecular charge transfer transition is greater compared to the ground state. Further, the emission spectra increased gradually upon increasing the solvent polarity, this was due to the charge separation upon excitation. In close examination the emission spectra of these compounds are broad and red shifted as the solvent polarity increases. This red shift is associated with increase in the electron donating ability of substituent. The D-π-A (donor- π system-acceptor) push-pull system charter of ICT effect is more prominent between terminal donor substituent and an acceptor carbonyl group of compound 4g. As a result, the polarity of compounds increases on excitation. Moreover, stabilization of highly dipolar excited state in polar solvents confirm the presence of π-π* transitions in 4g. It is concluded that emission spectra is more sensitive to solvent polarity compared to absorption spectra, which indicates that photoinduced intramolecular charge transfer (ICT) occurs in the singlet excited state from the strong electron donating substituent –OCH_3 group to the electron acceptor carbonyl group of chromophore [31-33]. We believe that these chalcone heterocyclic molecules may find potential applications as new fluorescent probes or luminescence materials and biological.

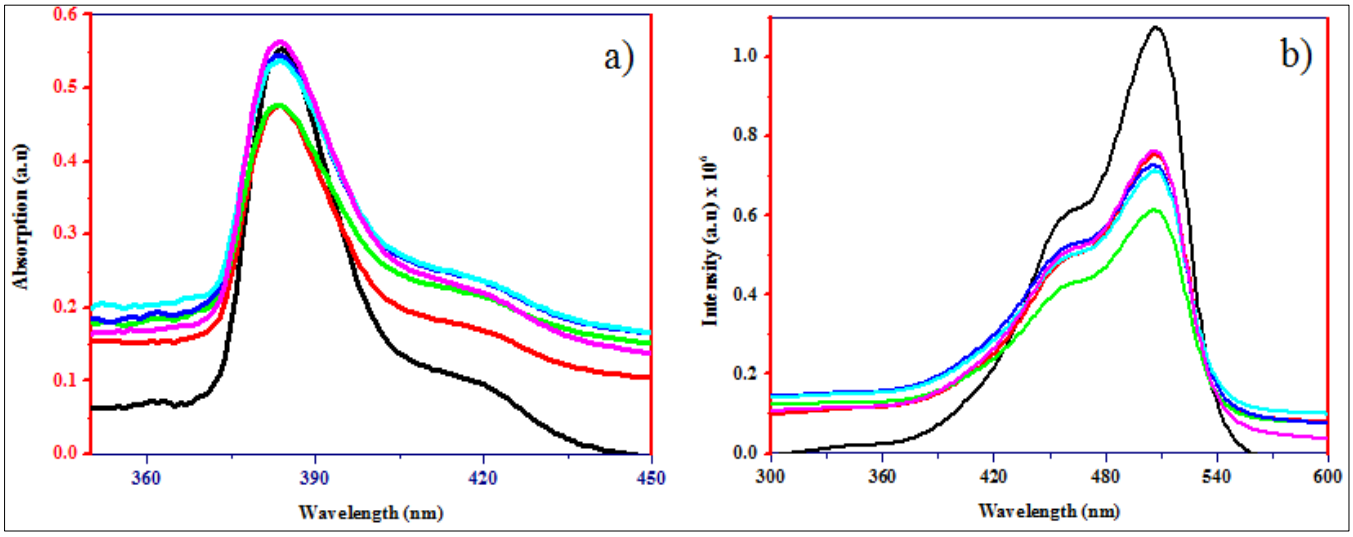


Fig 3 Absorption and emission spectrum of compound 4g in different solvents

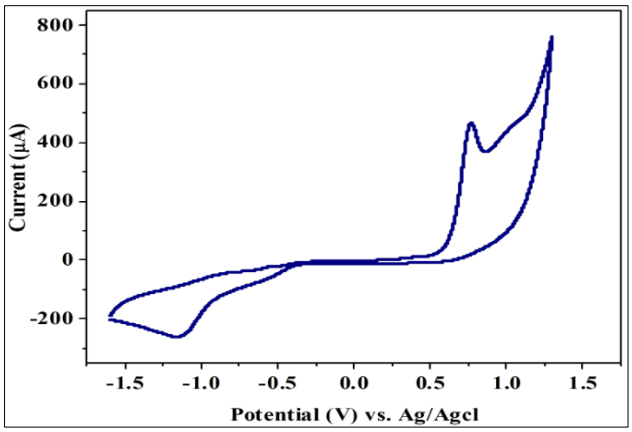


Fig 4 CV spectrum compound of 4g in 0.1 M (Bu_4PF_6) /CH_3OH, scan rate of 100 Mvs-1

Electrochemical studies

The cyclic voltammetry (CV) spectrum compound of 4g carried out by a glassy carbon working electrode, a platinum wire counter electrode and saturated calomel as a reference electrode in acetonitrile with the presence of tetrabutylammonium hexafluorophosphate (Bu_4PF_6) as supporting electrolyte at a scan rate of 100 Mvs-1. The glassy carbon, platinum wire and silver wire served as the working, counter and reference electrodes respectively in (Fig 4).

The oxidation peak potential of compound 4g are 0.768eV and reduction potential suggesting that the successive formation of the cation radical should be attributed to the donating ability of electrons from the -OCH_3 groups. The electrochemical behavior of 4g shows the oxidation process to be irreversible, while the reduction presents a sharp peak attributable to a one electron transfer reduction of carbonyl group [34]. The HOMO energy levels of compound 5g as -0.2420eV and LUMO energy levels of compound 4g are -0.0897eV, is due to presence of electron donating ability of the -OCH_3 is carried out by DFT methods in (Fig 5). The calculated ground-state geometries demonstrate that intramolecular charge transfer (ICT) occurs in molecules during the procedure of charge excitation from HOMO to LUMO. Generally, high charge mobility containing molecules (D-π-A) have strong intramolecular charge transfer.

CONCLUSION

Isoindolinone derivatives have been synthesized with different donor and acceptor substituted in phenyl group. Molecular docking of most active compounds 4a, 4b, 4c, 4d, 4g exhibit most binding affinity with EGFR target receptor. Absorption and emission spectrum of compound 4g fabricate an intramolecular charge transfer maxima at 510 nm. ICT Characteristic of absorption and fluorescence properties shows increasing the polarity of solvents with the quantum yield. The irreversible oxidation potential of isoindolinone 4g was observed at 0.768eV. DFT study also good agreement with electrochemical properties of chalcone compound 4g gives one electron transfer reduction of carbonyl group. These outcomes widen the scope of pulle push result on photoluminescent and it will provide as an important for the synthesis of fluorescent probe.

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