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Computational Elucidation of Novel Synthetic Scheme for Erlotinib

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ABSTRACT

The current study focusses on the use of quantum chemistry to elucidate the novel synthetic route for e mrlotinib from methyl 4,5-dihydroxy-2-isocyanobenzoate, which includes oxidative coupling, nucleophilic addition, cyclization and Williamson's ether synthesis. The overall reaction requires three intermediate and produces 13 transition states [TS]. Which are less than the earlier reported synthetic schemes. The energies of each reactant, intermediate and products were calculated using DFT (density functional theory) and B3LYP/6-311+G* as a basis set. The energies diagram obtained indicates the novel proposed scheme could follow the easy path to obtain the product, moreover, the energy barrier required to overcome the transition state is low indicating, very less activation energy is required for every reactant to take part in chemical reaction.

Keywords: Erlotinib, Non small cell lung cancer, Synthesis, quantum chemistry, Density functional theory, Basis set, Minimization, Activation energy.

INTRODUCTION

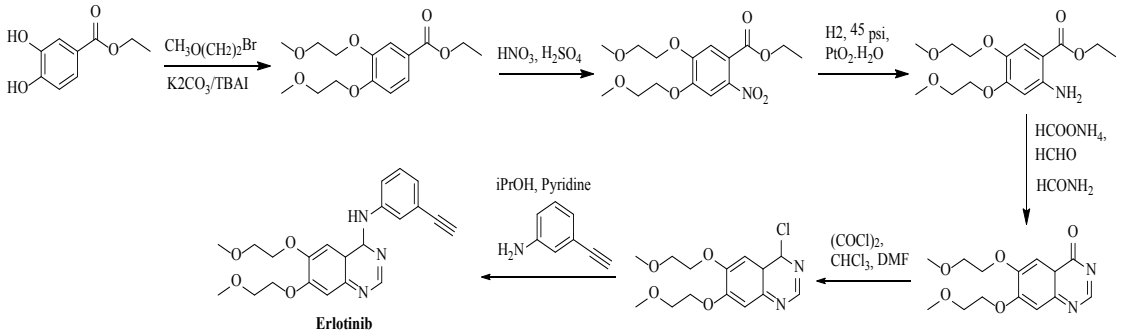
Erlotinib is a targeted therapy used in the treatment of non-small cell lung cancer (NSCLC) and pancreatic cancer. It belongs to the class of drugs known as tyrosine kinase inhibitors (TKIs), specifically targeting the epidermal growth factor receptor (EGFR)[1–3].

EGFR is a protein involved in regulating cell growth and division. In cancers like NSCLC and pancreatic cancer, EGFR can be overactive, leading to uncontrolled cell growth. Erlotinib works by inhibiting the tyrosine kinase activity of EGFR, thereby blocking the signalling pathways that promote cancer cell growth and proliferation. Clinical studies, such as the pivotal BR.[21] trial for NSCLC, have demonstrated the efficacy of erlotinib in improving progression-free survival and overall survival in certain patient populations, especially those with EGFR mutations[4,5]. Additionally, it has shown benefits in advanced pancreatic cancer, either as a single agent or in combination with other chemotherapy drugs[6].

Quantum chemistry plays a pivotal role

in elucidating reaction mechanisms by providing detailed insights into the molecular-level processes involved in chemical reactions. It involves applying principles of quantum mechanics to study the behaviour of atoms and molecules, their interactions, and the distribution of electrons within them[7]. Quantum chemistry contributes to understanding reaction mechanisms. it is widely used in calculating energies, geometries of reactants, intermediates, transition states, and products involved in a reaction. Understanding these structures and their energy changes helps identify stable and transient species and elucidate the energy profiles of reactions. It also helps in determine transition states-the fleeting states between reactants and products[8–10]. By characterizing transition states, researchers can assess activation energies and reaction rates, crucial for understanding reaction mechanisms. Quantum calculations provide information about bond energies, bond lengths, and electron densities involved in bond-breaking and bond-forming processes during reactions. Quantum chemistry helps to explore various possible pathways a reaction might take. Calculations reveal the most favourable routes and intermediates, aiding in understanding the sequence of steps involved in a reaction. It also provides mechanistic insights by analysing electronic structures, charge distributions, and orbital interactions, quantum chemistry offers mechanistic insights, explaining how electrons rearrange and how molecular properties change during a reaction[11]. In summary, quantum chemistry provides a theoretical framework to understand reaction mechanisms by exploring molecular structures, energies, transition states, and electronic properties. These computational methods complement experimental observations, aiding in the elucidation and prediction of complex chemical reactions[12].

The common method for erlotinib consist of six to seven steps starting from[3,4], dihydroxy benzoic acid or its derivatives as mentioned in Scheme 1. The key intermediates and their preparations involve a series of reaction and use of highly flammable gas such as hydrogen at high pressure, and platinum oxide a costly reagent[13,14].



Scheme 1. Reported synthesis of Erlotinib

Keeping the drawback of known synthetic schemes we propose a new scheme can shorten the reaction steps and can lead to the higher yield of the product, in addition the new scheme eliminates the danger associated with the use of flammable catalyst such as hydrogen gas[15].

MATERIAL AND METHODS

The chemical structures and the reaction mechanism were drawn using ChemDraw and saved in mol2 format. All quantum calculations were performed using Gaussian 09 program suit. Structures (reactants, intermediates and products) were optimized to locate the minima. Transition states were identified by finding only one negative eigenvalue. B3LYP/6-311+G* level was used to optimize the reaction pathway followed by single-point calculations at MP2 level using the same basis set. Solvent influence on relative energies of the reactants, intermediates and transition states is also calculated at MP2/6-311+G*:PCM//B3LYP/6- 311+G level using continuum solvent model. The relative energies of the species were calculated with respect to the starting material 4,5-dihydroxy-2-isocyanobenzoate[16].

RESULT AND DISCUSSION

The reaction mechanism involves four major steps and proceeds with three intermediate formations.

Overall reaction proceeds with stages involving cyclization, halogenation followed by Williamson synthesis and finally amination or C-N coupling. Schematic reaction path is depicted in Figure 1.

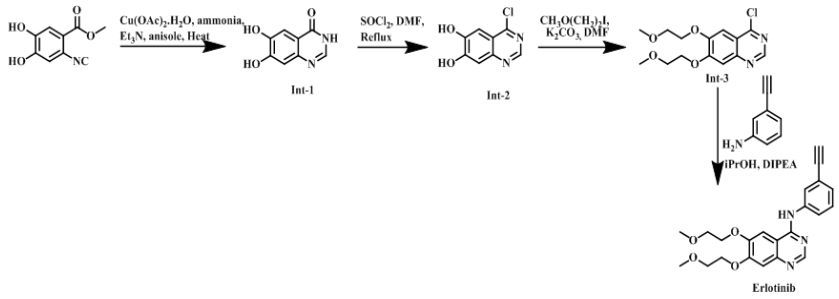


Fig. 1. Schematic reaction pathway for the synthesis of erlotinib

Cyclization

This step consists of various sub steps starting from oxidative coupling in which partially negative carbon atom of iso thiocyanate is attacked by diacetoxycopper to form a bond between copper and partially charged carbon, which is then attacked by ammonia base to undergo nucleophilic addition reaction followed by reductive elimination and generation of various transition states which are in resonance with each other. These resonating structure/transition states undergo intramolecular cyclization mediated by ammonia to form intermediate-1. The schematic representation for the synthesis of intermediate-1 is shown in Fig. 2. The starting material was minimized using aforementioned method, energy obtained for the compound-I was -82.1 Kcal/mol, whereas as observed from energy diagram compound-I is unstable (97.3 Kcal/mol) and immediately releases energy to converted in compound-III which is quite stable (-152.2 Kcal/mol). Compound-IV absorbs the energy and is converted to TS-1 (180.5 Kcal/mol), the energy difference between compound-3 and TS-1 is -332.7 Kcal/mol indicating the reaction is endothermic and requires energy. The two transition states formed, TS-1 and TS-II shows somewhat similar energy indicating both the structures are unstable and are interconvertible, their energy values are 180.5 Kcal/mol and 179.8 Kcal/mol respectively. The formation of Int-1 from TS-II is exothermic in natures, releases about 269.4 Kcal. mol heat which is highly stable. The overall energy diagram for the formation of Int-1 from compound-1 is shown in Figure 3.

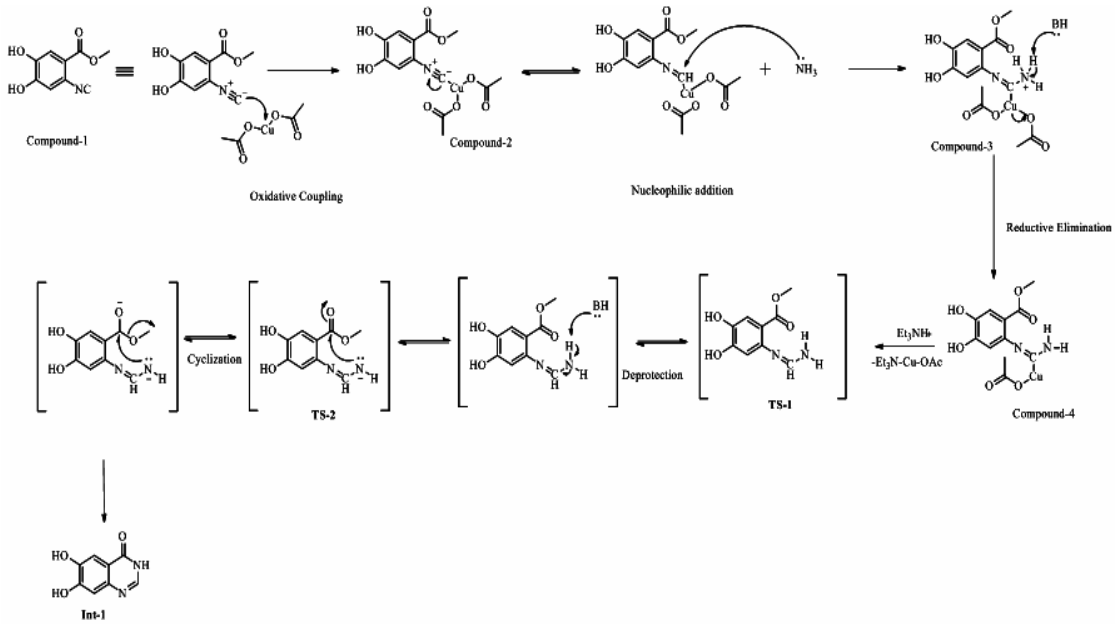


Fig. 2. Schematic reaction pathway for the synthesis intermediate (Int) 1

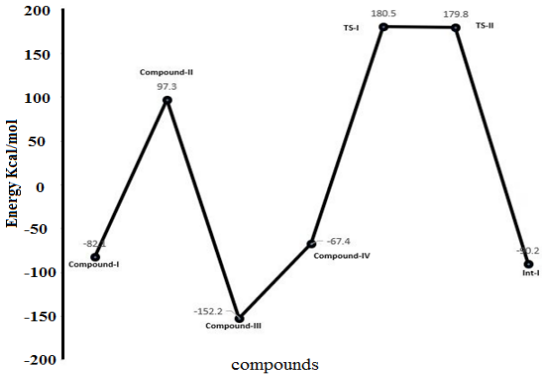


Fig. 3. Energy diagram for the formation of Int-1 from Compound-1

Halogenation

6,7-dihydroxyquinazolinone and its resonating structures undergo nucleophilic attack via sulphonyl chloride to form an unstable compound TS-3, loss of one chlorine atom results in compound TS-4, which further undergo nucleophilic attack to form TS-5 followed by intermolecular rearrangement to form Int-2. Schematic representation of overall cyclization process in given in Fig. 4. As per the energy diagram enormous amount of heat is absorbed to form three unstable transition state compounds. The energy diagram for the three transition states are 87.8 Kcal/mol, 102.2 Kcal/mol and 130.8 Kcal/mol for TS-II, TS-III and TS-IV respectively. As discussed, these intermediates undergo further changes to form stable compound Int-2 (-80.4 Kcal/mol). The energy diagram for the formation of Int-II from Int-I is shown is Figure 5.

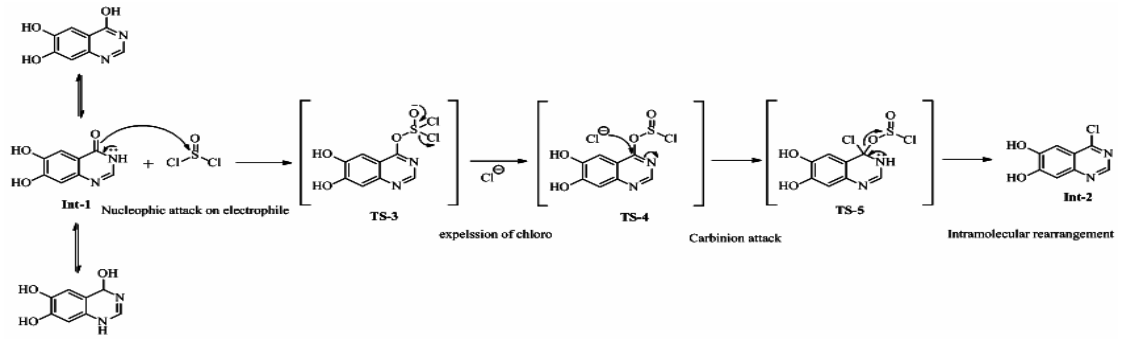


Fig. 4. Schematic reaction pathway for the synthesis intermediate (Int) 2

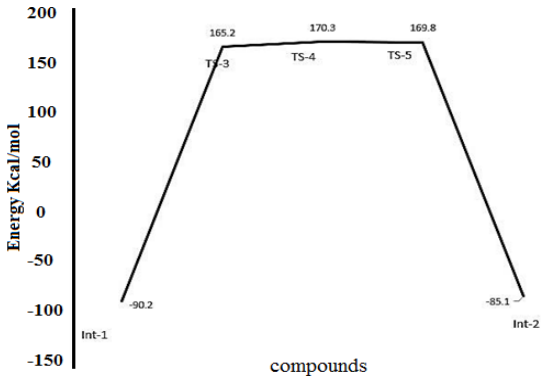


Fig. 5. Energy diagram for the formation of Int-2 from Int-1

Williamson ether synthesis

Usually it involves SN2 reaction where an alkoxide ion interacts with primary alkyl halide. Reaction of Intermediate-2 with ammonia and potassium carbonate result in the formation of unstable compound which eliminates 2 mol of hydrogen carbonate (HCO_3). The product formed thus react with 2 mol of KI and undergo SN2 reaction to form Int-3. Schematic representation of overall reaction process in given in figure 6. Similar to Int-2 formation, formation of Int-III generates four unstable transition states, TS-6, TS-7, TS-8 and TS-9 with the energy of 95.2 Kcal.mol, 98.8 Kcal/mol, 93.2 Kcal/mol and 108.4 Kcal/mol respectively. These TS states undergo reaction with potassium iodide to form stable Int-3 (-91.8 Kcal/mol). The energy diagram for their formation shown is Figure 7.

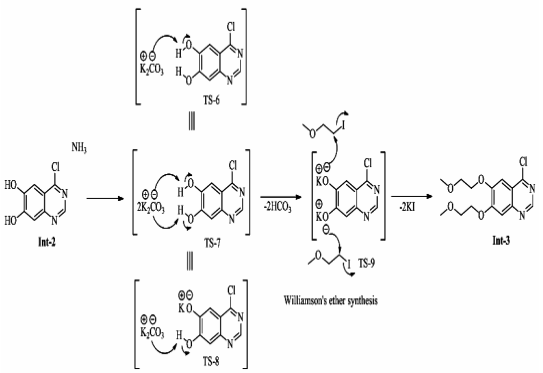


Fig. 6. Schematic reaction pathway for the synthesis intermediate Int-3

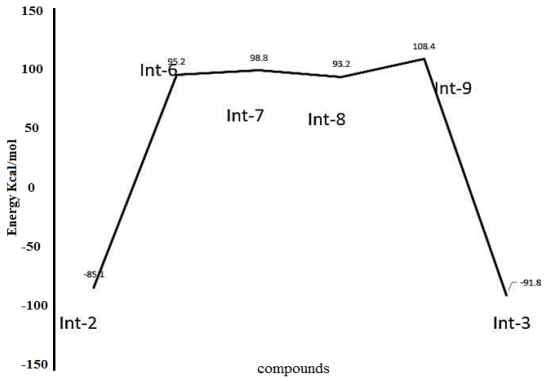


Fig. 7. Energy diagram for the formation of Int-3

Amination (nucleophilic aromatic substitution)

Intermediate-3 reacts with 3-ethynylaniline to form TS compound which undergo rearrangement to form Erlotinib. Schematic representation of overall reaction process in given in Fig. 8. The formation of erlotinib from Int-3 proceeds with the formation of three Transition states compounds. TS-10, TS-11, TS-12 with the energy of 87.8 Kcal/mol, 102.2 Kcal/mol, 130.8 Kcal/mol. The final product (erlotinib) shows the energy of -80.4 Kcal/mol, which is quite stable shown in Figure 9.

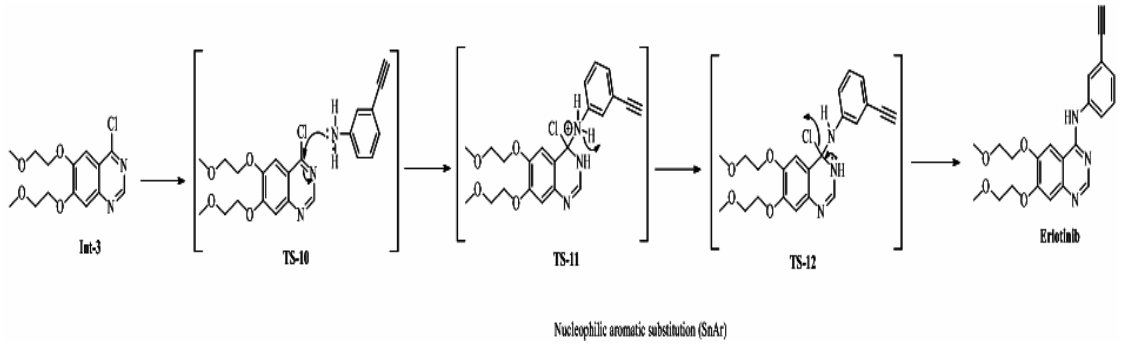


Fig. 8. Schematic reaction pathway for the synthesis of erlotinib

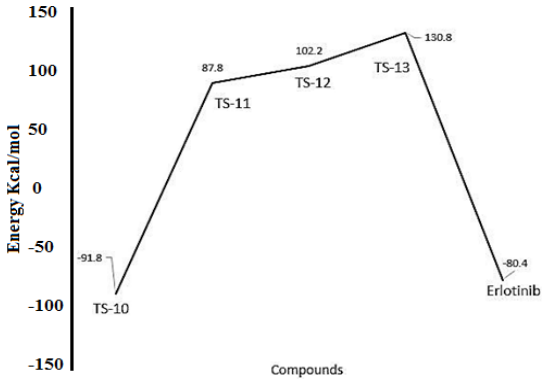


Fig. 9. Energy diagram for the formation of Erlotinib

CONCLUSION

Erlotinib, (Tarceva), is a reversible and extremely selective EGFR tyrosine kinase inhibitor. It is used to treat pancreatic cancer and non-small cell lung cancer (NSCLC).[4] It is specifically used to treat NSCLC caused by mutations in the EGFR (epidermal growth factor receptor). In 2004, erlotinib received FDA approval for use in medicine. It is included in the List of Essential Medicines by the World Health Organization. The reported synthetic schemes of Erlotinib consist of six-seven steps, which are highly expensive. Moreover, use of flammable catalysts and hydrogen gas in the current synthesis process again raise the associated safety concerns. In the current manuscript, we propose a new synthetic scheme for the preparation of erlotinib. This novel scheme undergo the product formation in fewer steps and does not require or produce any harmful reagents or byproducts. We validated the scheme by calculating the energies using Quantum calculations. The current proposed scheme could be adopted in the synthesis of erlotinib.

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Conflict of interest

The author declare that we have no conflict of interest.

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