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Elucidating Reaction Mechanism of Gefitinib- An Anticancer Drug by Computational Technique

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ABSTRACT

The present investigation centres on the application of quantum chemistry to clarify the innovative synthetic pathway for Gefitinib derived from methyl 2-isocyano-4,5-dimethoxybenzoate. This pathway encompasses various chemical reactions such as cyclization, halogenation, regioselective demethylation, Williamson's ether synthesis, and nucleophilic aromatic substitution. The reaction necessitates the presence of four intermediate species and yields a total of 11 transition states [TS]. The energies of each reactant, intermediate, and product were determined through the utilisation of density functional theory (DFT) with B3LYP/6-311+G(d) serving as the basis set. The energy diagram that was obtained shows that the new plan that was suggested could follow an easy path to obtaining the product.

Keywords: Gefitinib, Quantum chemistry (QM), Density Functional Theory (DFT), Transition states (TS). Cyclization, Halogenation, Regioselective demethylation.

INTRODUCTION

Gefitinib is an effective small-molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase[1,2]. EGFR belongs to the class of targeted therapies known as tyrosine kinase inhibitors (TKIs), it is a transmembrane receptor that regulates cell proliferation, survival, and differentiation. EGFR overexpression or mutation is common in multiple types of cancers, particularly non-small cell lung cancer (NSCLC), making it an attractive target for therapy[3-6]. In 2003, the United States Food and Drug Administration (FDA) approved gefitinib as the first EGFR inhibitor for the treatment of patients with advanced NSCLC who had previously failed to respond to chemotherapy[7]. Its approval represents a significant advance in the treatment landscape for NSCLC, offering a targeted therapy option for patients with specific EGFR mutations. Gefitinib works by selectively binding to the EGFR tyrosine kinase domain's adenosine triphosphate (ATP) binding site, which inhibits receptor autophosphorylation and downstream signalling cascades. Gefitinib inhibits cancer cell growth and induces apoptosis by inhibiting EGFR-mediated signalling pathways involved in cell proliferation, survival, and angiogenesis[8,9].

A substantial portion of the knowledge regarding reaction mechanisms is gained through the utilisation of quantum chemistry, which offers intricate insights into the molecular-level processes underlying chemical reactions. It entails investigating the behaviour, interactions, and electron distribution of atoms and molecules through the application of quantum mechanics principles[10,11]. The study of quantum chemistry can facilitate comprehension of reaction mechanisms. It is extensively employed in the determination of the geometries and energies of reactants, intermediates, transition states, and products during a chemical reaction[12]. Gaining comprehension of these configurations and the fluctuation in their energy assists in the differentiation of stable and transient constituents, in addition to clarifying the energy profiles of reactions. It can also be utilised to identify transition states, which are temporary states that exist between reactants and products. Researchers can ascertain activation energies and reaction rates, which are crucial for comprehending reaction mechanisms, through the characterization of transition states[13]. The bond energies, bond lengths, and electron densities implicated in the bond-forming and bond-breaking mechanisms of reactions are disclosed through quantum calculations. Quantum chemistry facilitates the investigation of an extensive range of potential reaction pathways. By revealing the most favourable pathways and intermediates, calculations facilitate comprehension of the reaction's step sequence. Through the examination of orbital interactions, charge distributions, and electronic structures, quantum chemistry additionally imparts mechanistic insights. It describes how molecular properties change and electrons rearrange during a reaction[14-16]. In summary, quantum chemistry provides a conceptual structure through which reaction mechanisms can be comprehended through the examination of electronic properties, molecular structures, energies, and transition states. In addition to experimental observations, these computational methods aid in the comprehension and forecasting of intricate chemical reactions.

Several steps are required to synthesise gefitinib, which typically begins with commercially available starting materials[17]. Although the particulars of proprietary synthetic routes may differ among pharmaceutical companies, the synthesis of such complex molecule is accompanied by multiple obstacles. Such as low yield, complexity of intermediates, scalability, cost, and regulatory compliance. One such example is synthesis of the molecule using 4-aniline quinazoline group which requires extra steps that made the process inefficient and uneconomical. While acknowledging the limitations of existing synthetic schemes, we present a novel approach and scheme that has the potential to reduce reaction time and increase product yield.

Methodology

All the chemical structures of reaction mechanism were drawn on ChemDraw and saved in mol2 format. Gaussian16 software was utilized to conduct quantum calculations. The local minima were obtained by optimising the structures of reactants, intermediates, and products. Transition states were determined using negative eigenvalue. All the structures were optimized using B3LYP/6-311+G(d,p) basis set. Single-point calculations were performed at the MP2 level utilising the identical basis set. Additionally, the continuum solvent model is employed to compute the influence of the solvent on the relative energies of the reactants, intermediates, and transition states at the MP2/6-311+G(d,p):PCM//B3LYP/6-311+G(d,p) level.[18,19]

RESULT AND DISCUSSION

The reaction mechanism involves five major steps and proceeds with four intermediate formations. Overall reaction proceeds with stages involving cyclization, halogenation followed by regioselective demethylation, Williamson's ether synthesis and finally Nucleophilic aromatic substitution (Figure 1)

The energies calculated in the synthesis of Gefitinib are reported in Table1.

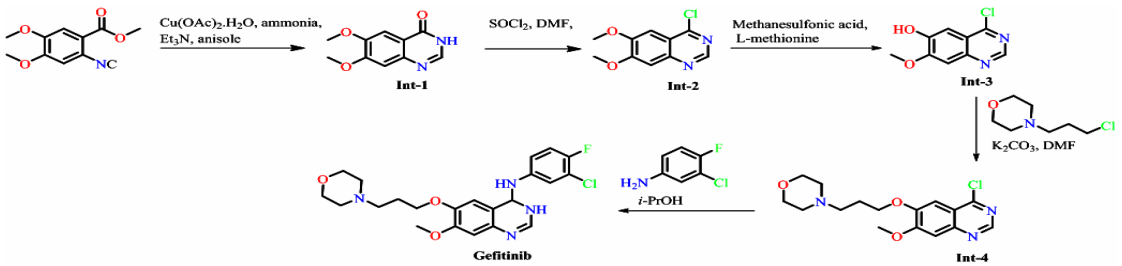

Fig. 1. Proposed novel scheme for Gefitinib synthesis

Table 1: Optimization energy for overall reaction in Gefitinib synthesis

Compound ID	Energy (Kcal/mol)	Compound ID	Energy (Kcal/mol)
Compound-I	-81.8	INT-III	-75.2
INT-I	-79.2	INT-IV	-73.9
INT-II	-78.4	Gefitinib	-69.8

Cyclization

The first step involves the coordination of copper acetate with electron-deficient methyl-2-isocyano-4,5-dimethoxybenzoate to form compound-II complex. The formed cupper complex undergoes nucleophilic attack by ammonia to forms compound-III. The Comp. III further undergoes reductive elimination passes through TS-I and TS-II. Here Base-catalysed deprotonation and intramolecular cyclization results in the formation of Int-1.

The schematic representation for the synthesis of intermediates-1 is shown in Fig. 2. Starting materials was optimized using the B3LYP/6-311+G(d,p) basis set using Gaussian16. Optimization energy for the compound-I was found to be -81.8 Kcal/mol. Compound-II shows higher energy (102.4Kcal/mol) compared to compound-I indicating endothermic reaction, Fig. 3. Formation of compound-III is mediated by release of enormous energy. The energy for compound-III was found to be -98.3Kcal/mol. Compound-III undergo deprotonation and cyclization to form TS-I and TS-II (transition state) showing energy of 175.4kcal/mol and 176.8kcal/mol energy. Unstable transition states molecule rearranges to for stable intermediate-I (Int-I) with an energy value of 79.2kcal/mol. Graphical representation of energy diagram is shown in Figure 3.

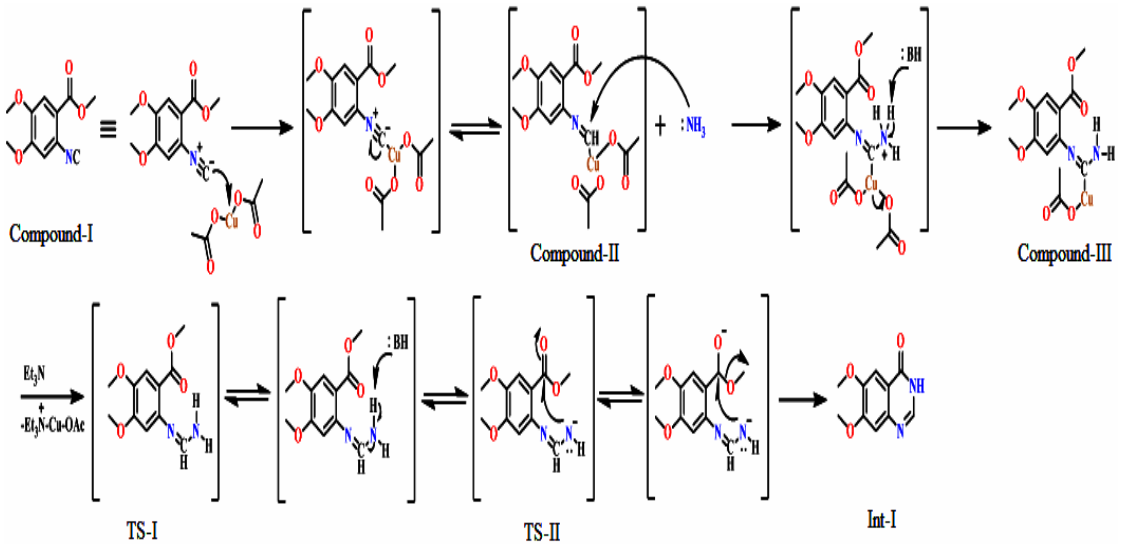

Fig. 2. Proposed reaction for the synthesis intermediate-I (Int-I)

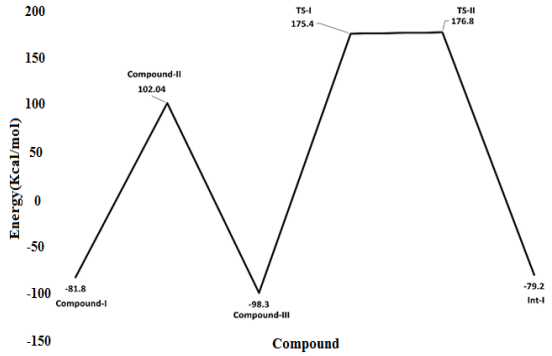

Fig. 3. Potential energy diagram for the formation of Int-1

Halogenation

In the second step we propose chlorination of 6,7-dimethoxyquinazolin-4-one using readily available thionyl chloride as chlorinating agent. Nucleophilic attack via pi bond of carbonyl carbon on sulphur electrophile (of thionyl chloride) forms unstable chlorosulphite complex TS-1. Nucleophilic attack of chloride ion on carbonyl carbon forms unstable TS-2 and TS-3 with the elimination of SO_2Cl as byproduct (Fig. 4). Finally, deprotection of proton by chloride ion afford Int-II. All the transition state molecules involved in halogenation process shows nearly same energy and are unstable and releases energy to form Int-II (Figure 5).

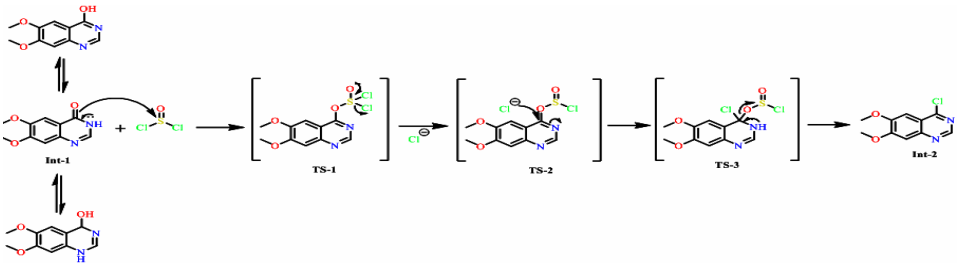

Fig. 4. Proposed reaction mechanism for the intermediate-II (Int-II)

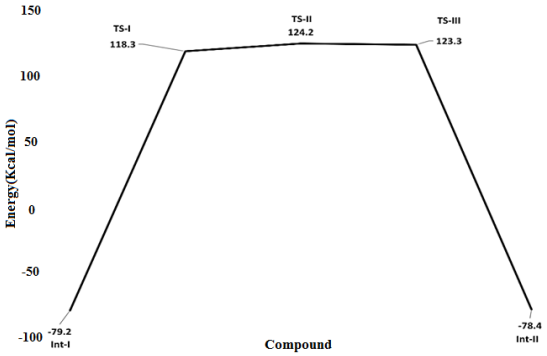

Fig. 5. Potential energy diagram for the formation of Int-II

Regioselective demethylation

We propose regioselective demethylation of 4-chloro-6,7-dimethoxyquinazoline (Int-II) using methane sulphonic acid to afford 4-chloro-7-methoxy-quinazolin-6-ol (Int-III). In third step, lone pair of oxygen attacks the hydride ion of sulfonic acid to form TS-1. Formed TS-1 undergoes nucleophilic attack by carbanion of sulfonic acid to afford unstable TS-2, which collapse to generate Int-3 (Fig. 6). The energy diagram (Fig. 7) indicates the highly unstable nature of compounds thereby releasing energy to form Int-III.

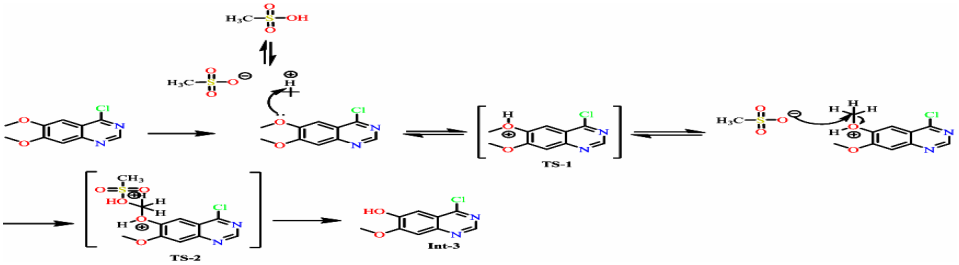

Fig. 6. Proposed reaction mechanism for the intermediate-III (Int-III)

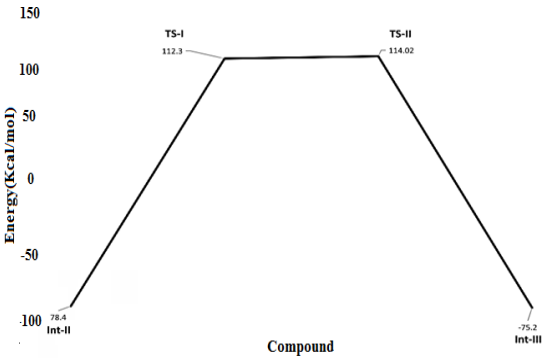

Fig. 7. Potential energy diagram for the formation of Int-III

Williamsons ether synthesis

Fourth step for the synthesis of Gefitinib as per proposed scheme involves *O*-alkylation of 4-chloro-7-methoxy-quinazolin-6-ol (Int-3) using 4-(3-chloropropyl) morpholine. Carbonate carbanion (-CO_3) generated from K_2CO_3 abstract proton from 6-hydroxy group of Int-III to form TS-I. The formed oxygen anion in TS-I attacks on 4-(3-chloropropyl) morpholine *via* SN2 reaction mechanism to afford Int-IV with the elimination of potassium chloride as a byproduct (Fig. 8). Energy calculation of Int-IV shows lower energy as compared to Int-III (Figure 9).

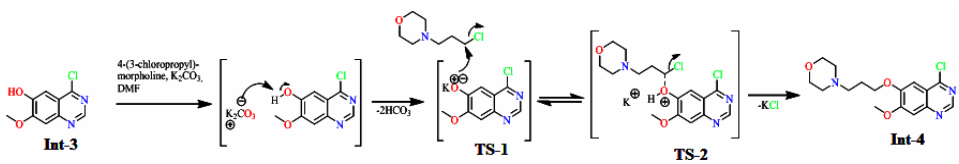

Fig. 8. Proposed reaction mechanism for the formation of intermediate-IV (Int-IV)

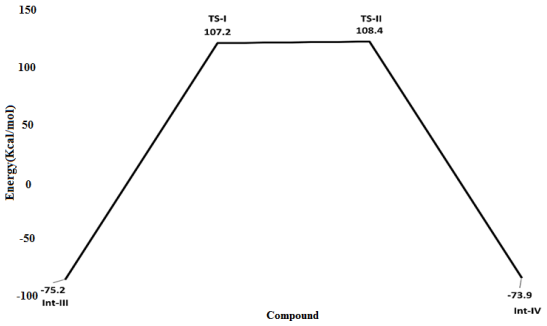

Fig. 9. Potential energy diagram for the formation of Int-IV

Nucleophilic aromatic substitution

The step fifth follows the nucleophilic aromatic substitution reaction in between Int-IV and 3-chloro-f-fluoroaniline. Nucleophilic amine (aniline) attack and form two consecutive transition state TS-1 and TS-2 which on ultimately breaks C-Cl bond and form new C-N bond to afford Gefitinib (Fig. 10). It was observed, the TS state shows less energy in the final stage as compared to the transition state formed in the early stage. Also, the energy found for Gefitinib was lower as compared to starting material (Figure 11).

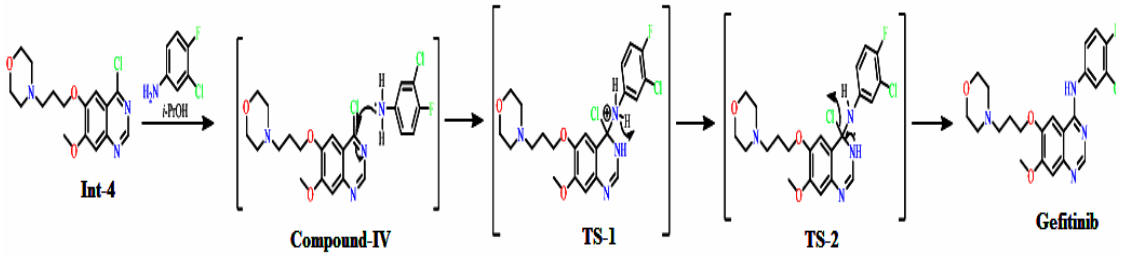

Fig. 10. Proposed reaction mechanism for the formation of Gefitinib

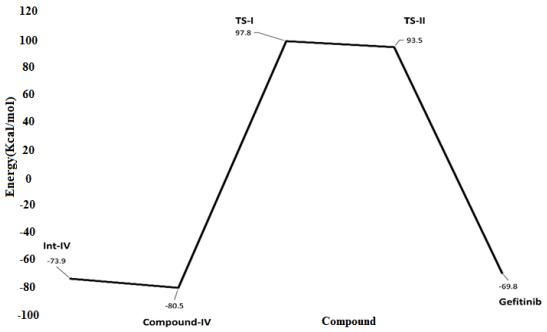

Fig. 11. Potential energy diagram for the formation of Gefitinib

CONCLUSION

In 2003, the U.S. Food and Drug Administration (FDA) approved Gefitinib as the initial EGFR inhibitor for treating patients with advanced NSCLC who have not responded to previous chemotherapy. The approval of this treatment represents a notable progression in the field of non-small cell lung cancer (NSCLC), providing a focused therapeutic alternative for individuals with particular EGFR mutations. Synthesis of Gefitinib involves the use of complex starting materials or intermediates, which could present challenges in their availability, cost or scalability. Current scheme proposes a new synthetic route for the preparation of Gefitinib, this novel scheme may undergo the product formation in fewer steps and high yield.

We validated our scheme computationally by calculating the energies using quantum calculations. The current proposed scheme could be adopted in the synthesis of Gefitinib.

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Conflict of interest

There are no conflicts of interests.

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