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Original article

Synthesis and theoretical studies on energetics of novel N- and O- perfluoroalkyl triazole tagged thienopyrimidines – Their potential as adenosine receptor ligands

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ABSTRACT

A series of novel N- and O- perfluoroalkyl triazole tagged thienopyrimidines **6a–c** and **7a–d** was synthesized in two steps from thienopyrimidin-4-ones **2** through O- and N-propargylated regioisomers **3a–i** and **4a–i** respectively. Compound **2** was reacted with propargyl bromide to form O- and N-propargylated regioisomers **3** and **4** in definite proportions. Each regioisomer was separated and independently subjected to [3 + 2] cycloaddition using perfluoroalkyl azides through Click reaction under Sharpless conditions and obtained exclusively *anti* product in each case. The formation of two regioisomers in the first step and single *anti* addition product in the next step could be explained based on computational studies carried out at B3LYP/6-31G(d) level of theory. Results of Fukui function indices at the reactive centers are in accordance with the observations. On evaluation of the synthesized molecules for their binding affinities towards adenosine receptors, 4**d** and 4**f** were found to be selective to A_1 over A_{2A} receptors.

1. Introduction

The bioisosteric replacement of benzene ring with π-excess thiophene has been an established ligand-based drug design strategy to optimize various lead structures. Diverse functionalized thiophene derivatives were reported as adenosine receptor ligands for the past twenty years [1–3]. Thiophene fused pyrimidines called thienopyrimidines exhibit DHFR inhibitory [4] CDK4 inhibitory [5], anti-inflammatory [6] activities. Several quinazolines and thienopyrimidines were reported from our laboratory as antihistaminic [7] antibacterial [8] bronchodilatory [9], anti-inflammatory agents [10] and as adenosine receptor ligands [11].

Based on the importance and in continuation to our investigations, we report the synthesis of novel derivatives with thienopyrimidine nucleus. Since five-membered rings with more number of nitrogens like tetrazole, triazole and imidazole is found to be the best ranked substitutions in antagonizing a wide variety of macromolecular targets [12], we attempted to synthesize O, N- propargylated thienopyrimidines and 3/4-triazolyl thienopyrimidines. Such a non-classic isosteric modification of triazolo thienopyrimidines is done to evaluate them for adenosine binding activity. Perfluorinated alkyl chain was selected to increase the lipophilicity of molecules in order to cross the blood brain barrier. The synthesis of title compounds was performed using Cu(I)-catalyzed Huisgen [3 + 2] dipolar cycloaddition reaction between an organic azide and an alkyne commonly known as click chemistry. This reaction has several applications in chemistry, biology and materials science. It has enabled demanding bio-conjugations involving more number of steps and has been used in activity-based protein profiling (ABPP) of crude proteome homogenates for selective labeling of modified bacterial cell walls and in the synthesis of novel biologically active compounds [13–15]. Initially the synthesis of O-/N-propargylated thienopyrimidines was carried out and the variation in the product yield is correlated with the substituent at the 2nd position. Position and orientation of attack of reagent on the transition state of the staring material was predicted with the help of chemoinformatics to elucidate the observed synthetic trends. Further, existence of two reactive nitrogens in perfluoroalkyl azide in reaction with alkyne can lead to the formation of 1, 4 and 1, 5-disubstituted alkyl [1–3] triazoles through their *syn* and *anti* additions. But, formation of only 1,4-disubstituted triazole in considerable yields along with

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remaining amount of starting material in the experimental studies led us to use density functional theory to unravel the experimental observations. Molecular modeling studies were carried out and the reactants, products and transition states were optimized at B3LYP/6–31G* level of theory as B3LYP with 6–31G* basis set is proved to be better in modeling the reactions [16]. IRC calculations were performed to characterize the transition states. Fukui function indices were calculated using the following equations

$$f_k^+ = [q_k(N+1) - q_k(N)] \text{ for nucleophilic attack} \quad (1)$$

$$f_k^- = \left[q^k(N) - q_k(N-1)\right] \text{ for electrophilic attack} \quad (2)$$

$$f_k^\bullet = [q_k(N+1) - q_k(N-1)] \text{ for free radical attack} \quad (3)$$

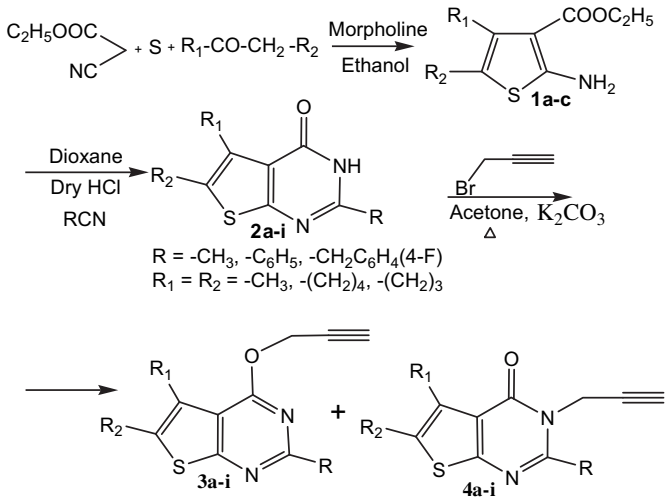
All the calculations were performed using G03W program [17]. The charge densities were obtained using AIM2000 program [18].

2. Results and discussion

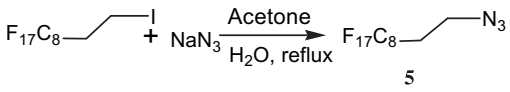
2.1. Chemistry

The initial step involves the synthesis of thiophene 2-amino-3-carboxylic acid ethyl ester **1** from cyanoethylacetate, ketone and sulfur in ethanol using morpholine as base [19]. Then preparation of thieno [2,3-*d*] pyrimidin-4(3H)-ones **2** from compound 1 and alkyl/aryl nitrile in dioxane using dry HCl [20]. The thieno [2,3-*d*] pyrimidin-4(3*H*)-ones **2** were reacted with propargyl bromide in acetone using potassium carbonate as a base to yield two products namely O- and N-propargylated thieno pyrimidines **3** and **4** in definite proportions [21] as outlined in Scheme 1. The formation of each regioisomer depends on the bulkiness/electron-withdrawing or donating nature of substituents present. The O-propargylated product **3** is formed in major when R is aromatic, while N-propargylated compound **4** is major when –R is aliphatic. In the second step, synthesis of various perfluoroalkyl azides **5** was performed as outlined in Scheme 2 [22]. All the products were separated through column chromatography and characterized based on their difference in polarity.

Further the O- and N-propargylated thienopyrimidines **3** and **4** were independently reacted with perfluoroalkyl azide **5** in THF, using copper (I) iodide as catalyst [23] and resulted in exclusively



Scheme 1. Synthesis of O- and N- propargylated thienopyrimidines **3** and **4.**



Scheme 2. Synthesis of perfluorinated alkylazides **5.**

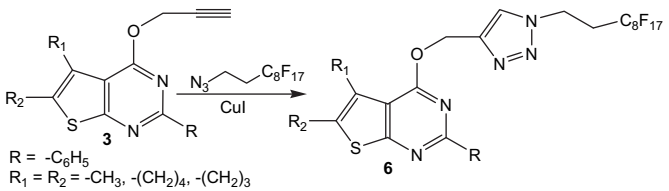
1,4-disubstituted-1,2,3-triazole derivatives **6** and **7**, respectively according to Schemes 3 and 4. The reaction is considered to take place via 1,3-dipolar cycloaddition of perfluoroalkyl azide to alkyne through a preformed copper acetylide complex formation [24,25]. The percentage yields of products tabulated in Tables 1 and 2. The cycloaddition reaction was also performed in DMSO in order to see the influence of solvent on the formation of products and found to give better yields.

2.2. Modeling studies

Molecular modeling studies were carried out in order to understand the observed synthetic trends. As the nature of substituent (–R_1 and –R_2 groups) seems to be inconsequential with respect to the observed yields of **3a–i** and **4a–i**, it was felt logical to replace them with H in all computational calculations.

From the experimental trends, the R group is mainly found to influence the site of attack of nucleophile which would result in formation of O- and N- propargylated thienopyrimidines **3** and **4** from thienopyrimidines **2**. Computational calculations were performed on thienopyrimidine **2** by taking R as H, –CH_3 or –C_6H_5, as representatives of unsubstituted, aliphatic (alkyl) and aromatic (aryl) groups respectively. Both gas phase and solvent calculations have been carried out on thienopyrimidine in order to examine the solvent dependency. The activation and reaction energies (in kcal/mol) for both gas and solvent phases are illustrated in Table 3. IRC calculations were performed to characterize the transition states which further confirmed the authenticity of transition states.

Initially the solvent effects on the reactivity were studied, followed by the comparison of reactivity of CH_3 and C_6H_5 substituted compounds with that of unsubstituted (H as substituent) compounds which is followed by the explanation for the site selective addition at N and O sites. From the data (Table 3) it can be understood that the addition of solvent decreases the activation energies and reaction energies (except for H substituted compounds). The H substituted compounds show increase in both activation and reaction energies compared to the CH_3 and C_6H_5 substituted compounds. Since variation in the yields seems to be mainly due to the aliphatic and aromatic groups, further studies were carried out based on the site selectivity at N and O positions. Also from the table, it can be inferred that the N-propargylated thienopyrimidine (**4**) with methyl substitution is found to be stable, both kinetically and thermodynamically. Replacement of –R with –C_6H_5 suggested the formation of kinetically stable O-propargylated thienopyrimidine and thermodynamically stable N-propargylated thienopyrimidines. However the difference between the activation energies for **2-A–Me** and **2-B–Me**, and **2-A–Ph** and **2-B–Ph** regioisomers in gas/solvent phases are 0.0/0.4 and 3.8/3.0



Scheme 3. Synthesis of O- perfluoroalkyl triazole tagged thienopyrimidines **6.**