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Pd-mediated functionalization of polysubstituted pyrroles: Their evaluation as potential inhibitors of PDE4

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ABSTRACT

Novel polysubstituted pyrroles have been designed and accessed via a one-pot multicomponent reaction followed by Pd-mediated C–C bond forming reactions. All the compounds synthesized were tested for their PDE4B inhibitory properties in vitro and two of them obtained via Heck reaction showed significant inhibition. The docking results suggested that these alkenyl derivatives containing ester moiety interact well with the PDE4B protein in silico where the ester carbonyl oxygen played a key role. The pyrrole framework presented here could be a new template for the identification of small molecule based novel inhibitors of PDE4. The single crystal X-ray data of a representative compound is presented.

The pyrrole derivatives constitute an important class of heterocycles found in many natural products such as heme, chlorophyll, vitamin B12, and various cytochromes.[1] In addition to their wide applications in organic synthesis[2] and materials science,[3] pyrrole derivatives have attracted particular attention in drug discovery due to their various pharmacological properties.[4] For example, anticancer drug candidate tallimustine and blockbuster cholesterol lowering drug atorvastatin (Lipitor) belongs to this class. Atorvastatin is presently one of the top-selling drugs worldwide.

Phosphodiesterase 4 has been identified as a valuable therapeutic target in a variety of conditions particularly inflammatory diseases. Inhibitors of PDE4 has been evaluated for the treatment of asthma and chronic obstructive pulmonary disease (COPD).[5] However, clinical studies of the first-generation PDE4 inhibitor rolipram were associated with the side effects including nausea and emesis that were thought to arise from inhibition of the PDE4D subtype.[6] Similarly, side effects have restricted the therapeutic index and consequently delayed the market launch of the second-generation PDE4 inhibitors cilomilast and roflumilast.[7a] Encouragingly, roflumilast (Daxas®, Nycomed) has been launched in Europe for the treatment of COPD recently. During clinical studies roflumilast in addition to its well-known anti-inflammatory effects has shown improvement of fasting blood glucose and hemoglobin A1C levels in patients with comorbid type 2 diabetes mellitus indicating beneficial effects of PDE4 inhibitors in diabetic patients.[7b] More recently, the discovery of the resveratrol-PDE link have suggested that PDE4 inhibitors, possibly in combination with other PDE inhibitors, may be useful for mimicking calorie restriction (CR) thereby treating aging-related diseases.[7c] All these observations therefore have generated a renewed interest in the discovery and development of novel inhibitors of PDE4 possessing fewer side effects. Since recent studies have indicated that among the four subtypes, for example, A, B, C and D the PDE4B subtype is linked to inflammatory cell regulation[8] hence it was hypothesized that selective inhibition of the PDE4B may provide a means to achieve efficacy while potentially mitigating the adverse effects.[9]

A variety of heterocyclic structures has been explored for the discovery of novel PDE4 inhibitors[5,10] including pyrroles.[10b] For example, MNP001 (**A**, Fig. 1)[11] a pyrrole based small molecule is being developed to dually inhibit PDE4 and antagonize L-type calcium channels with the aim that additive/synergistic action of reducing Ca^{2+} influx and increasing intracellular cyclic AMP level would lead to vascular smooth muscle relaxation and reduction of peripheral resistance and blood pressure. Indeed, MNP001 has been found to have promising antihypertensive potency and

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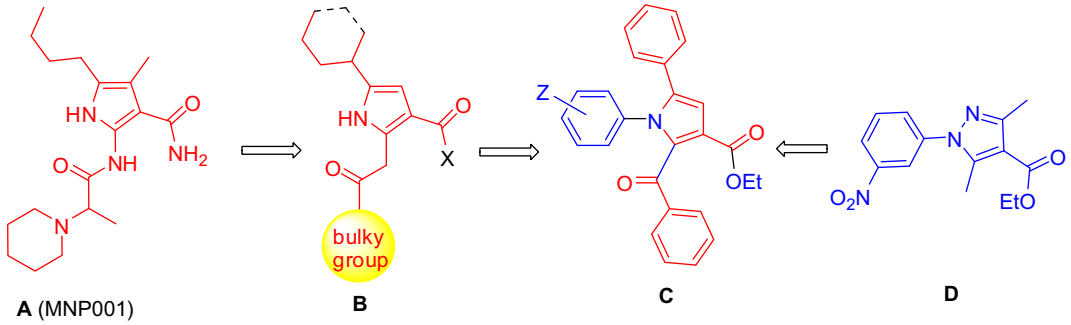
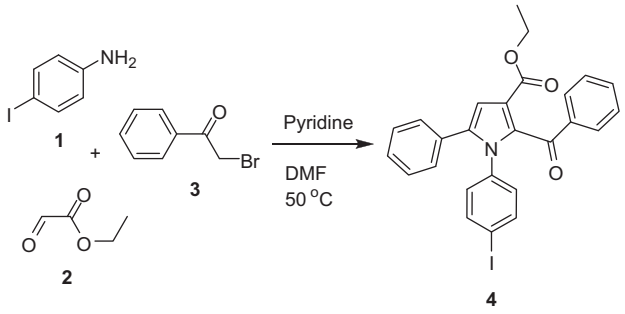


Figure 1. Design of pyrrole based new inhibitors (**C**) of PDE4.



Scheme 1. Synthesis of ethyl 2-benzoyl-1-(4-iodo)-5-phenyl-1*H*-pyrrole-3-carboxylate (**4**).

Table 1
Effect of reaction conditions on the MCR of **1**, **2** and **3**[a]

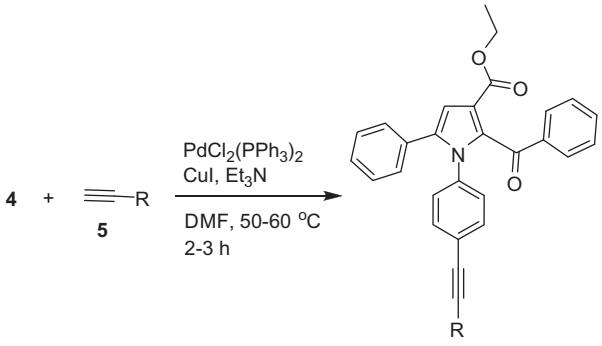
Entry	Solvent	Base	Temp (°C)	Time (h)	Yield[b] (%)
1	Acetonitrile	Pyridine	80	12	37
2	Toluene	Pyridine	110	24	24
3	1,4-Dioxane	Pyridine	100	24	trace
4	Acetonitrile + DMF (8:2)	Pyridine	80	10	42
5	DMF	Pyridine	80	8	41
6	DMF	Pyridine	50	10	53
7	DMF	Pyridine	25	24	10

[a] All the reactions were carried out using 4-iodo aniline **1** (1.0 mmol), ethyl glyoxylate **2** (1.0 mmol) and phenacyl bromide **3** (2.0 mmol) in the presences of a base (4.0 mmol).
[b] Isolated yield.

prolonged duration of action. Pyrazole containing N-substituted derivatives, for example, ethyl 3,5-dimethyl-1-(3-nitrophenyl)-1*H*-pyrazole-4-carboxylate (**D**, Fig. 1) on the other hand has been reported as inhibitor of PDE4.[12] Combining some of the structural features of **A** (via **B**) and **D** in a single molecule may lead to compound **C** (Fig. 1) which may serve as a new template for the identification of novel PDE4 inhibitors. Prompted by this hypothesis we initially became interested in the synthesis of **C** and subsequent evaluation of their PDE4 inhibiting properties in vitro. To the best of our knowledge PDE4 inhibiting properties of highly substituted pyrrole derivatives represented by **C** have not been explored earlier.

While versatile methodologies including conventional and transition metal catalyzed approaches[13] and more recently multi-component reactions[14,15] (MCRs) are available for the synthesis of pyrroles a straightforward preparation and functionalization of highly substituted pyrroles from readily available starting materials is still a challenge. Recently, an elegant MCR has been reported[16] for the synthesis of polysubstituted pyrroles structurally similar to **C** in moderate yields. We adopted a similar strategy to prepare our target compounds. The key starting material **4** required for our synthesis was prepared following a slightly modified method reported earlier (Scheme 1).[16] Initially, we conducted the one-pot reaction of 4-iodoaniline (**1**), phenacyl bromide (**2**), and ethyl glyoxylate (**3**) in the presence of pyridine in acetonitrile when the desired pyrrole derivative **4** was isolated in 37% yield (Table 1, entry 1). In order to improve the product yield we conducted the MCR under various reaction conditions (Table 1). Changing the solvent from acetonitrile to toluene or 1,4-dioxane

Table 2
Synthesis of ethyl 2-benzoyl-1-(4-alkynylaryl substituted phenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (**5**) via Sonagashira coupling of iodo pyrrole (**4**) and terminal alkynes (**5**)[a]



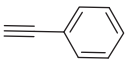
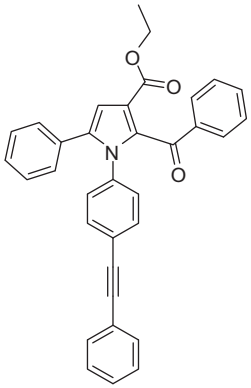
Entry	Alkynes (**5**)	Products[b] (**6**)	Yield[c] (%)
1	 **5a**	 **6a**	95
2	**5a**	**6a**	78[d]
3	**5a**	**6a**	70[e]

Table 2 (*continued*)

Entry	Alkynes (**5**)	Products[b] (**6**)	Yield[c] (%)
4	**5a**	**6a**	75[f]
5	**5b**	**6b**	92
6	**5c**	**6c**	85
7	**5d**	**6d**	88
8	**5e**	**6e**	89
9	**5f**	**6f**	92

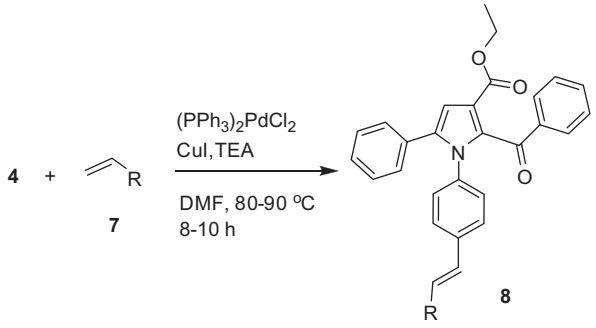
[a] All the reactions were carried out by using **4** (1 mmol), **5** (1.2 mmol), $(PPh_3)_2PdCl_2$ (0.02 mmol), CuI (0.02 mmol) and Et_3N (4 mmol) in DMF at 50–60 °C for 2–3 h under nitrogen.
[b] Identified by ^1H NMR, IR, and MS.
[c] Isolated yields.
[d] $Pd(PPh_3)_4$ was used as a catalyst.
[e] $PdCl_2$ was used as a catalyst.
[f] $Pd(OAc)_2$ was used as a catalyst.

did not improve the product yield (Table 1, entries 2 and 3). The use of a mixture of acetonitrile–dimethyl formamide (DMF) (8:2) provided **4** in 42% yield (Table 1, entry 4). We then examined the use of DMF alone at 80 °C but no improvement of yield was observed (Table 1, entry 5). Notably, lowering the temperature to 50 °C increased the yield to 53% (Table 1, entry 6). A further decrease in reaction temperature decreased the yield (Table 1, entry 7). All these reactions were performed using pyridine as a base whereas the use of piperidine or morpholine suppressed the product formation completely. Thus, the use of DMF-pyridine at 50 °C was found to be optimum for the present MCR.

We then focused on generating a library of small molecules represented by **C** (Fig. 1) via exploring the reactivity of the iodo group of **4** towards the Pd-mediated various C–C bond forming reactions. Thus, the iodo pyrrole **4** was initially reacted with phenyl acetylene (**5a**) in the presence of a Pd catalyst and CuI using Et_3N as a base in DMF at 50–60 °C under nitrogen. A number of Pd catalysts, for example, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PdCl_2$ and $Pd(OAc)_2$ were examined for this coupling reaction (Table 2, entries 1–4) among which $PdCl_2(PPh_3)_2$ was found to be the best in terms of product yield. A number of terminal alkynes were reacted with **4** in the presence of $PdCl_2(PPh_3)_2$ and CuI and results of this coupling reactions leading to various alkynyl derivatives **6a**–**f** are summarized in Table 2. It is evident from Table 2 that the present C–C bond forming reaction proceeded well irrespective of the nature of substituents present in alkyne **5** employed. All the target compounds were prepared in good to excellent yields.

Having prepared the alkynyl derivatives **6** successfully via Sonogashira reaction we then focused on Heck reaction of the iodo compound **4**. Thus the compound **4** was reacted with a number of alkenes (**7**) in the presence of $(PPh_3)_2PdCl_2$ and CuI using Et_3N in DMF at 80–90 °C under nitrogen. The reaction proceeded well irrespective of the alkenes employed and the corresponding alkenyl

Table 3
Synthesis of ethyl 2-benzoyl-1-(4-alkenyl substituted phenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (**8**) via Heck coupling of **4** and alkenes (**7**)[a]



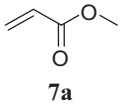
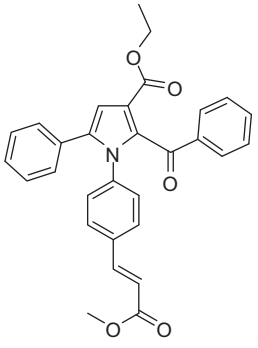
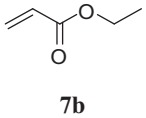
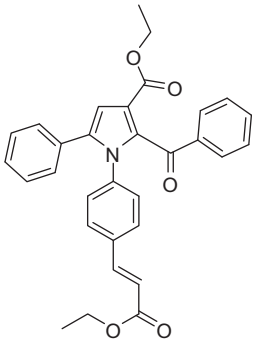
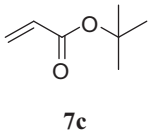
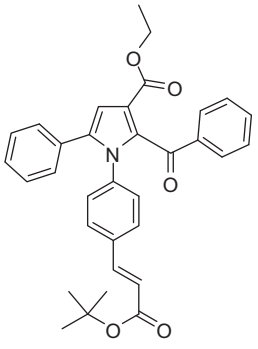
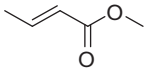
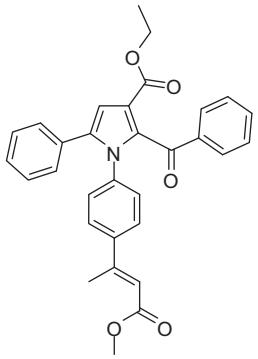
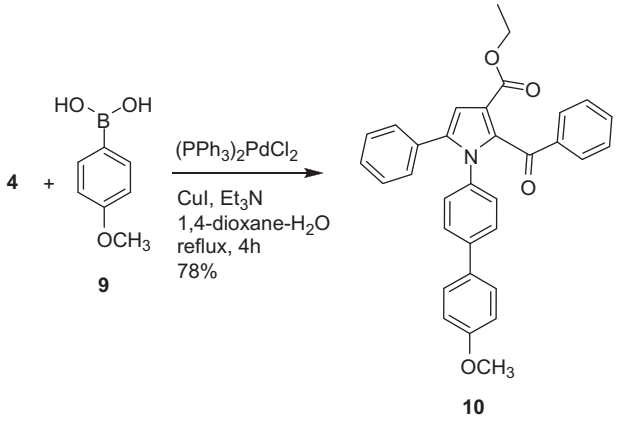
Entry	Alkynes (**7**)	Products[b] (**8**)	Yield[c] (%)
1	 **7a**	 **8a**	85
2	 **7b**	 **8b**	90
3	 **7c**	 **8c**	93

Table 3 (*continued*)

Entry	Alkynes (**7**)	Products[b] (**8**)	Yield[c] (%)
4	 **7d**	 **8d**	89

[a] All the reactions were carried out by using **4** (1.0 equiv), **7** (1.2 mmol), $(PPh_3)_2PdCl_2$ (0.02 mmol), CuI (0.02 mmol), and Et_3N (4 mmol) in DMF at 80–90 °C for 8–10 h.
[b] Identified by ^1H NMR, IR, and MS.
[c] Isolated yields.

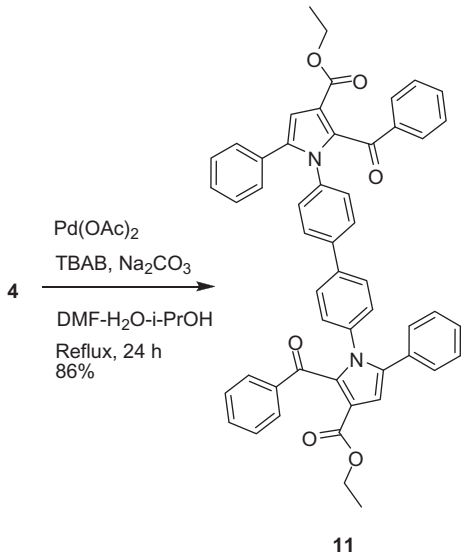


Scheme 2. Synthesis of ethyl 2-benzoyl-1-(4′-methoxybiphenyl-4-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate (**10**).

substituted products were isolated in good to excellent yields (Table 3).

Finally, iodo compound **4** was treated with an aryl boronic acid under Suzuki conditions to give the corresponding product **10** in good yield (Scheme 2). Notably, the compound **4** underwent homo-coupling reaction when treated with a Pd-catalyst in the presence of tetrabutyl ammonium bromide (TBAB) in 1:1:1 DMF:H_2O:*i*-PrOH affording the compound **11** (Scheme 3). The use of $Pd(OAc)_2$ afforded the best yield of compound **11** in compared to $Pd(PPh_3)_2Cl_2$.

While all the compounds synthesized were well characterized by spectral (NMR, IR and MS) data the compound **10** was selected for single crystal X-ray studies.[17] Accordingly, compound **10** was crystallized in the triclinic space group *P*-1with one molecule in



Scheme 3. Synthesis of diethyl 1,1′-(biphenyl-4,4′-diyl)bis(2-benzoyl-5-phenyl-1*H*-pyrrole-3-carboxylate) (**11**).

the asymmetric unit (Z = 2 Z' = 1) (Fig. 2). The molecule in the asymmetric unit does not have any conventional functional groups to form any strong hydrogen bonding (it contains ethyl ester and keto functional groups). However, the molecule in the asymmetric unit form dimer via C–H···O (C8–H8···O3, 2.46 Å 146°) synthon as shown in the Figure 3 along bc plane, which are very weak interactions. These interactions propagate in a 3D network kind of arrangement as shown in the Figure 4.

Having prepared a variety of highly substituted pyrrole derivatives we then tested these compounds for their PDE4B inhibitory properties in vitro.[18] All the compounds were tested at 30 μM using PDE4B enzyme isolated from *Sf*9 cells. Rolipram[19] was used as a reference compound in this assay. The results of this assay[20] for selected compounds are presented in Table 4. Notably, none of the alkynyl substituted pyrrole derivatives (**6**) showed significant inhibition of PDE4 and the data of a representative compound, that is, **6e** is shown in Table 4 (entry 1). In contrast, the alkenyl substituted pyrroles (**8**) showed better inhibition (Table 4, entries 2–5) among which the pyrrole derivative **8b** and **8d** were found to be promising (Table 4, entries 3 and 5). Like the alkynyl analogues **6** the pyrrole **10** obtained via Suzuki reaction did not show significant inhibition of PDE4B. All these observations suggested that the C-4 position of 1-phenyl ring of this class of pyrroles

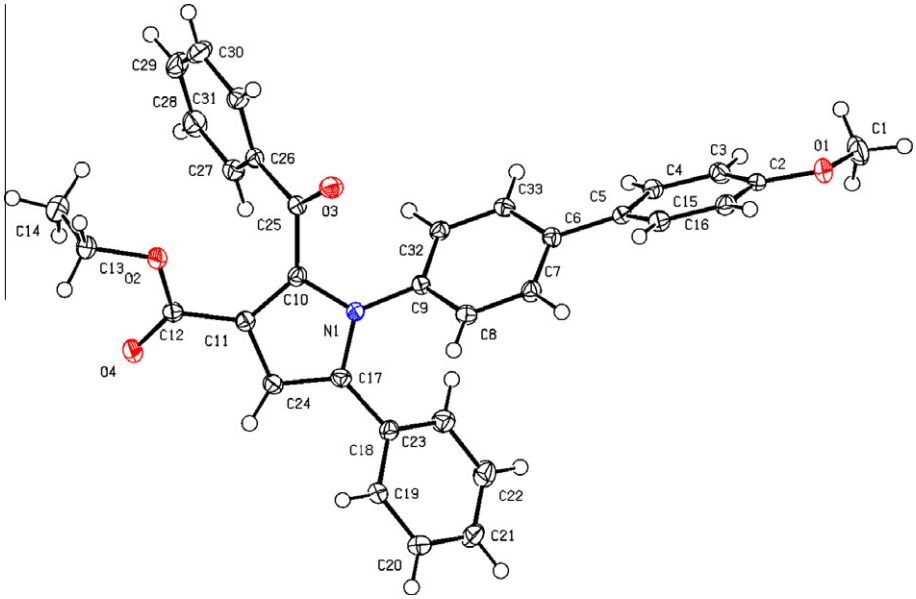


Figure 2. Showing the ortep diagram of compound **10** and thermal ellipsoids are drawn at 50% probability level.

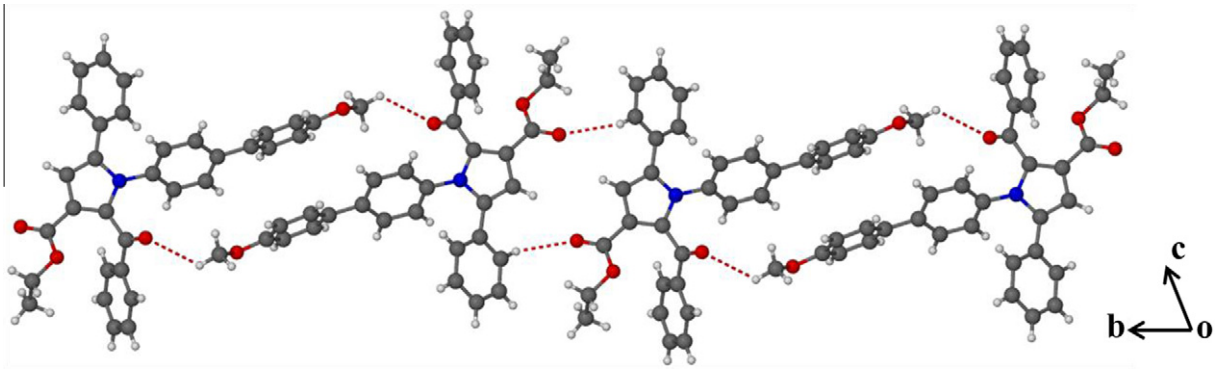


Figure 3. Showing the intermolecular hydrogen bonding formation via C–H···O synthon.

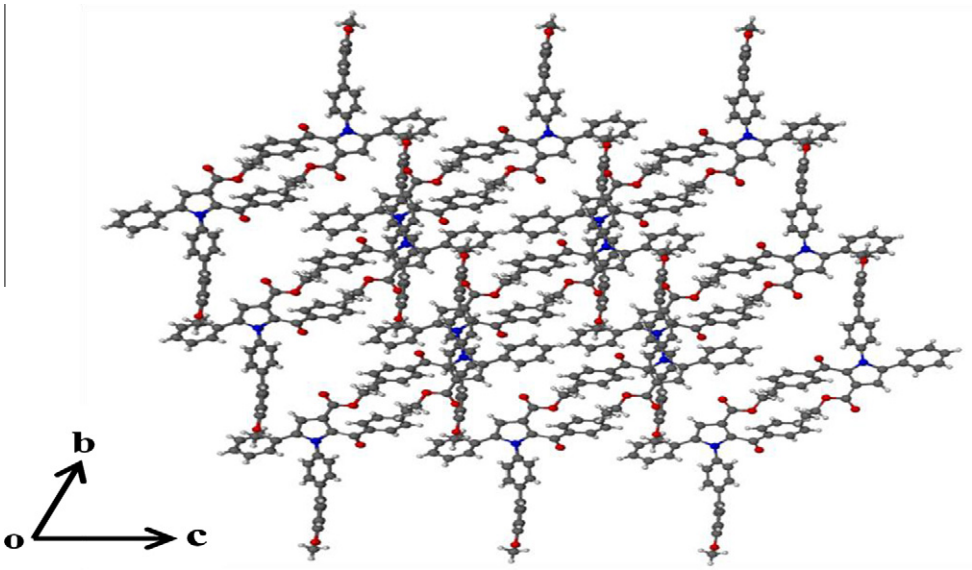


Figure 4. Showing the 3D network kind of arrangement.

Table 4
Inhibition of PDE4B by compound **6**, **8** and **10** at 30 μM

Entry	Compounds	Average% inhibition	SD
1	**6e**	22.14	2.72
2	**8a**	45.20	3.90
3	**8b**	74.71	0.86
4	**8c**	36.06	0.52
5	**8d**	76.74	1.12
6	**10**	24.78	1.21

SD = standard deviation.

seemed to be crucial where the presence of a linear alkynyl moiety or a bulky aryl group was not tolerated well. Among the alkenyl derivatives (**8**) tested the nature of ester group attached to the alkene moiety was found to be vital. For example, a bulky ester group, for example, *t*-butyl ester was found to be less suitable in terms of inhibitory activities. Nevertheless, the alkenes **8b** and **8d** were evaluated further for their PDE4B inhibiting potential. In a dose response study compound **8b** and **8d** showed dose dependent inhibition of PDE4B as shown in Figure5.

In order to understand the nature of interactions of these molecules with PDE4B docking studies were performed using the compound **8b** and **8d**. The GLIDE scores obtained after docking of these

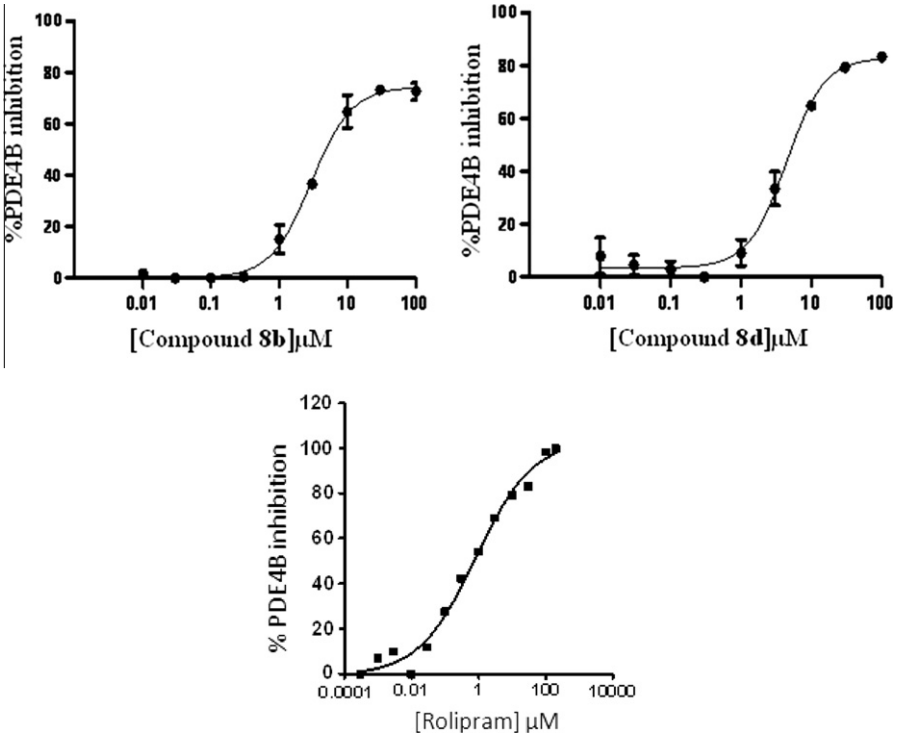


Figure 5. Dose response study of compounds **8b** and **8d** along with rolipram.

Table 5
Glide scores and other parameters of compounds after docking with PDE4B

Entry	Compound	Glide score	E-1[a]	E-2[b]	E-3[c]	E-4[d]	E-5[e]
1	**8b**	−9.28	−6.47	0	−1.59	0	−1.22
2	**8d**	−7.45	−4.47	−0.5	−0.34	−1	−1.14

[a] E-1 = Chemscore lipophilic pair term and fraction of the total protein-ligand vdw energy.
[b] E-2 = Hydrophobic enclosure reward.
[c] E-3 = Electrostatic reward.
[d] E-4 = Reward for hydrophobically packed H-bond.
[e] E-5 = Reward for hydrogen bond.

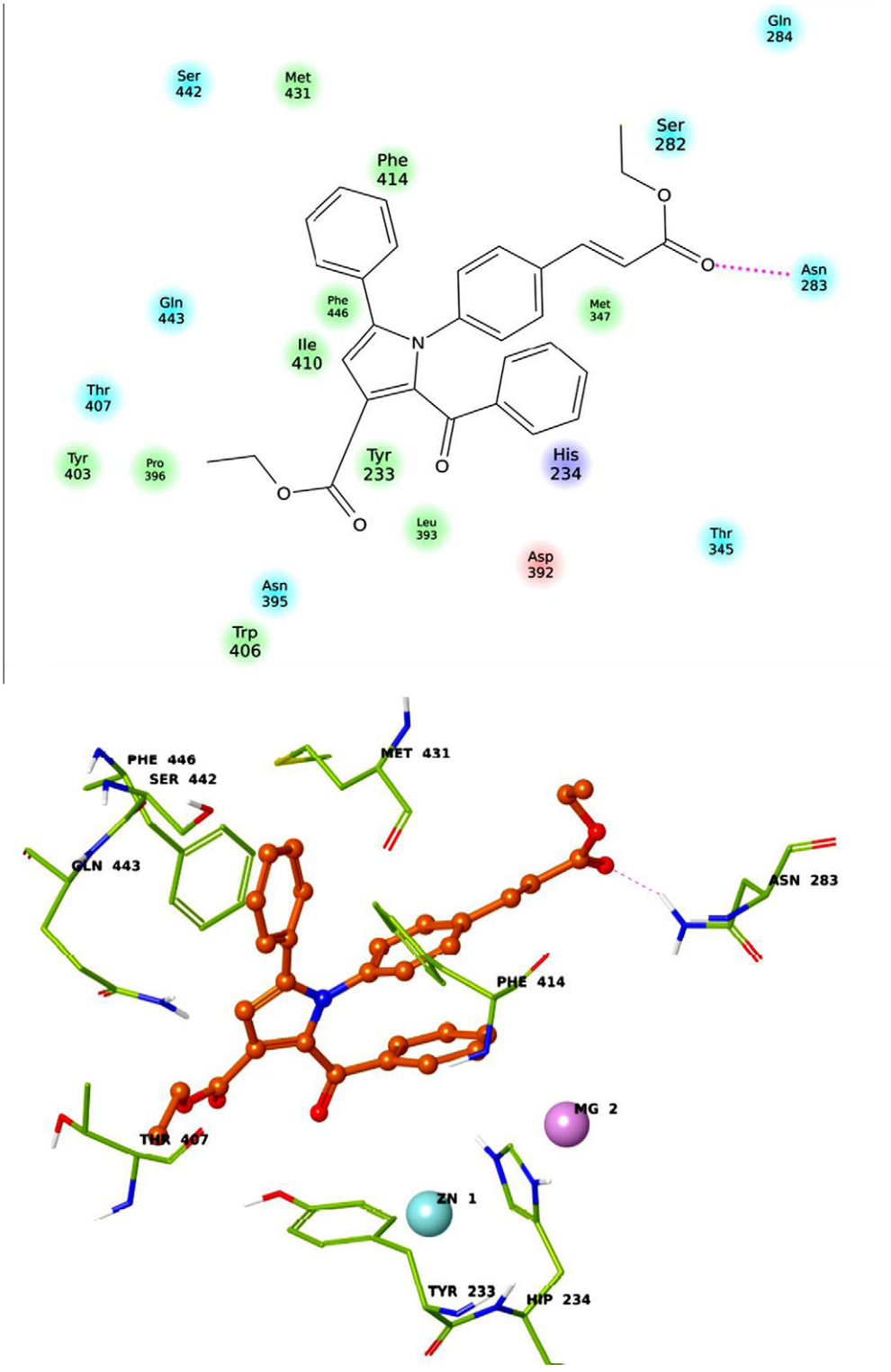


Figure 6. Docking of **8b** at the active site of PDE4B.

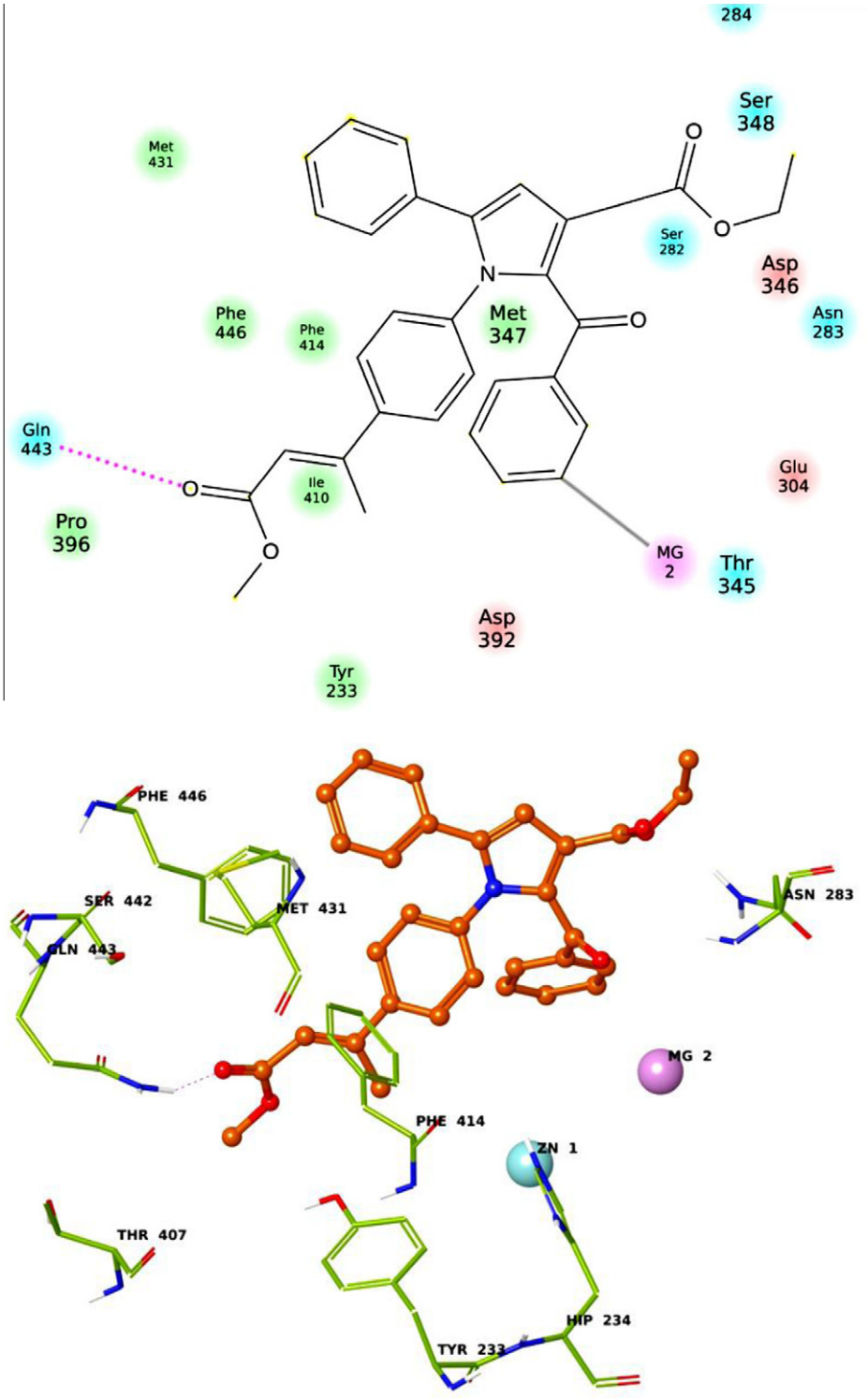


Figure 7. Docking of **8d** at the active site of PDE4B.

molecules with PDE4B protein are summarized in Table 5. The data shown in Table 5 clearly suggests that these molecules interact well with the PDE4B protein. The interaction of compound **8b** with the PDE4B protein (Fig. 6) was mainly contributed by an H-bonding between the amine group of asparagine 283 of the protein and the ester carbonyl oxygen of **8b**. Similarly, the interaction of compound **8d** (Fig. 7) was contributed by H-bonding between the amine group of glutamine 443 of PDE4B and the ester carbonyl oxygen of **8d**. Additionally, a π-cation interaction between the benzene ring of benzoyl group and the magnesium metal was observed in this case.

In conclusion, novel polysubstituted pyrroles have been designed as potential inhibitors of PDE4. All these derivatives were accessed via a one-pot MCR followed by Pd-mediated functionalization such as Sonogashira, Heck or Suzuki reactions. The second step, that is, C–C bond forming reactions proceeded well affording a variety of functionalized polysubstituted pyrroles in good yields. Single crystal X-ray data of a representative compound is pre-

sented. All the compounds synthesized were tested for their PDE4B inhibitory properties in vitro and two of them obtained via Heck reaction showed significant inhibition. The docking results suggested that these alkenyl derivatives containing ester moiety interact well with the PDE4B protein in silico where the ester carbonyl oxygen played a key role. Overall, the pyrrole framework presented here could be a new template for the identification of small molecule based novel inhibitors of PDE4.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.06.100.

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20. *PDE4B enzymatic assay*: The inhibition of PDE4B enzyme was measured using PDElight HTS cAMP phosphodiesterase assay kit (Lonza) according to manufacturer's recommendations. Briefly, 10 ng of PDE4B enzyme was pre-incubated either with DMSO (vehicle control) or compound for 15 min before incubation with the substrate cAMP (5 μM) for 1 h. The reaction was halted with stop solution followed by incubation with detection reagent for 10 min in dark. Luminescence values (RLUs) were measured by a Multilabel plate reader (Perklin Elmer 1420 Multilabel counter). The percentage of inhibition was calculated using the following formula: % inhibition = [(RLU of vehicle control—RLU of inhibitor)/(RLU of vehicle control)] × 100.