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Novel 1-alkynyl substituted 1,2-dihydroquinoline derivatives from nimesulide (and their 2-oxo analogues): A new strategy to identify inhibitors of PDE4B

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ABSTRACT

A number of novel 1-(3-arylprop-2-ynyl) substituted 1,2-dihydroquinoline derivatives related to nimesulide and their 2-oxo analogues have been designed as potential inhibitors of PDE4. All these compounds were synthesized by using Sonogashira coupling as a key step. In vitro PDE4B inhibitory properties and molecular modeling studies of some of the compounds synthesized are presented.

Phosphodiesterase type 4 (PDE4), one of eleven isozymes of cyclic nucleotide phosphodiesterases (PDEs) exists in four different isoforms (PDE4A, B, C and D). It is specific for the hydrolysis of cAMP to AMP in mast cells, basophils, eosinophils, monocytes, and lymphocytes as well as areas in the brain and airway smooth muscle.[1–4] The elevated levels of cAMP on the other hand are associated with the inhibition of cellular responses, including the production and/or release of proinflammatory mediators, cytokines, and active oxygen species in inflammatory cells. Thus inhibition of PDE4B suppresses inflammatory cell function *via* increasing the intracellular concentration of cAMP in the airway tissues and cells. The PDE4 inhibitors therefore are beneficial for the treatment of inflammatory and immunological diseases including asthma and chronic obstructive pulmonary disease (COPD).[1,4–6] While a number of inhibitors have shown promising results in clinical trials many of them are either dropped or halted due to the undesired side effects such as nausea, emesis,[1–3,5–8] and cardiovascular complications.[9a] Experimental data suggests that PDE4B is the main subtype that promotes inflammation whereas inhibition of PDE4D may cause emesis.[9b] It is therefore necessary to search for novel chemical class for the identification of PDE4B selective inhibitors as targeting PDE4B may be useful for the treatment of COPD and asthma without causing or minimizing the emetic side effects. Herein we report a new strategy to identify novel inhibitors of PDE4B namely 1-(3-arylprop-2-ynyl)-1,2-dihydroquinoline derivatives based on nimesulide.

A variety of heterocyclic structures has been explored for the discovery of novel PDE4 inhibitors[1,10] including *N*-alkyl substituted quinazolinone. For example, 4-(3-chlorophenyl)-1,7-diethylquinazolin-2(1*H*)-one or YM-976 (**A**, Fig. 1) that belongs to this class was identified as a potent inhibitor of PDE4 and showed promising results in animal models.[10a] Alkyne derivatives represented by general formula **B** (Fig. 1) on the other hand has been reported as inhibitors of PDE4.[11] Combining some of the structural features of **A** and **B** in a single molecule may lead to a new class of compound **C** (Fig. 1) which may be explored 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.

The key starting material **1** required for our synthesis was prepared following a reported method (Scheme 1).[12] Thus Vilsmeier–Haack cyclization of *N*-phenylacetamide (**2**) followed by hydrolyzing the resulting chloro compound in a mixture of acetic acid–water provided the quinolinone derivative **3** which on treatment with propargyl bromide afforded the expected terminal alkyne **1**.

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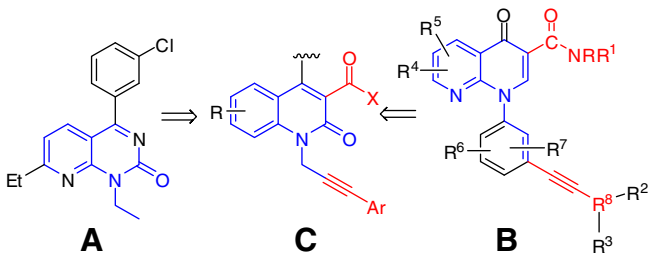
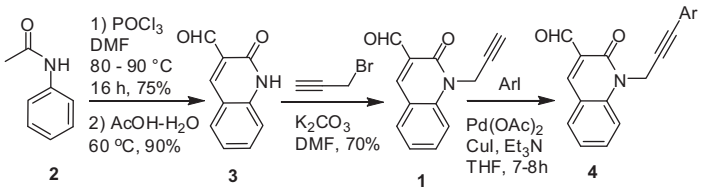


Figure 1. Design of new PDE4 inhibitors (**C**) based on known inhibitors **A** and **B**.

The alkyne **1** was reacted with a number of aryl iodide (Scheme 1) in the presence of $Pd(OAc)_2$ and CuI using Et_3N as a base in THF at 50–55 °C under nitrogen.[13] The reaction did not proceed in the absene of CuI. The use of $(i\text{-}Pr)_2NEt$ in place of Et_3N decreased the product yield. Notably, to the best of our knowledge Sonogashira coupling using alkyne **1** is not common in the literature.[14] The results of our palladium-catalyzed reaction leading to various alkynyl derivatives **4a–f** are summarized in Scheme 1 (the last step). It is evident from Scheme 1 that the present C–C bond forming reaction proceeded well irrespective of the nature of substituents present in alkyne **1** or aryl iodides employed. All the target compounds were prepared in moderate to good yields.

Due to our interest in the synthesis of quinoline based compounds of potential pharmacological interest we have recently reported the synthesis of 1,2-dihydroquinoline-based compound derived from an anti-inflammatory agent nimesulide.[15] Combining the structural features of these compounds with dihydroquinolines **4** (or **C**) we planned to synthesize compounds **7** as a new strategy to identify inhibitors of PDE4B. Accordingly, the compound **5** was reacted with propargyl bromide to give the terminal alkyne **6** which on Sonogashira coupling with aryl iodides under the condition as mentioned earlier provided the desired product **7** (Scheme 2). A number of aryl iodides were reacted with the alkyne **6** smoothly to give the aryl coupled product **7** without generating any significant side products. The groups such as $NHSO_2Me$ and OPh present in compound **6** and NO_2, Cl and CO_2Me present in aryl iodide were well tolerated.

Most of the compounds synthesized were tested for their PDE4B inhibitory properties in vitro at 30 μM using PDE4B enzyme assay[16] (Table 1). Rolipram[17] was used as a reference compound in this assay. In the case of 1-(3-arylprop-2-ynyl)quinolinone series (**4**) the presence of an ortho substituted aryl group attached with the alkynyl moiety was found to be benefecial (Table 1, entries 5 and 6) than other aryl substituents (Table 1, entries 1–4). However, a similar substituent effect was not observed in the case of 1-(3-phenylprop-2-ynyl)-1,2-dihydroquinoline series (**7**) (Table 1,



Ar =

p-$NO_2C_6H_4$- (**4a**; 65%),

m-$NO_2C_6H_4$- (**4b**; 74%)

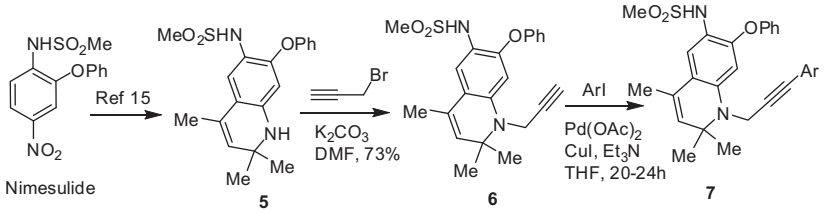
p-ClC_6H_4- (**4c**; 70%)

p-$MeOC_6H_4$- (**4d**; 75%)

o-ClC_6H_4- (**4e**; 72%)

o-$CH_3C_6H_4$-(**4f**; 70%)

Scheme 1. Preparation of key alkyne **1** and its use in the preparation of **4**.



Ar =

p-$NO_2C_6H_4$- (**7a**; 80%),

m-$NO_2C_6H_4$- (**7b**; 75%)

o-ClC_6H_4- (**7c**; 65%)

o-$MeOCOC_6H_4$- (**7d**; 75%)

o-$NO_2C_6H_4$- (**7e**; 65%)

C_6H_4- (**7f**; 77%)

Scheme 2. Synthesis of 1-(3-arylprop-2-ynyl)-1,2-dihydroquinolines derived from nimesulide.

Table 1
Inhibition of PDE4B by compound **4** at 30 μM

Entry	Compounds	Average% inhibition	SD
1	**4a**	4.15	0.93
2	**4b**	22.57	3.10
3	**4c**	26.53	5.80
4	**4d**	22.56	4.50
5	**4e**	54.37	6.60
6	**4f**	45.49	5.90
7	**7a**	35.07	0.05
8	**7b**	41.64	5.90
9	**7c**	40.28	3.39
10	**7d**	33.15	5.53
11	**7e**	37.40	4.73

SD = standard deviation.

Table 2
Glide scores and other parameters of compounds after docking with PDE4B

Entry	Compd	Glide score (K cal/mol)	E-1[a] (K cal/mol)	E-2[b] (K cal/mol)	E-3[c] (K cal/mol)
1	**4e**	−10.67	−4.67	−0.67	−0.17
2	**4f**	−10.71	−4.58	−0.67	−0.16
3	**7b**	−10.81	−6.72	−1.45	−0.64
4	**7c**	−10.62	−6.50	-1.90	−0.22
5	**7d**[d]	−8.64	−6.39	−1.73	−0.61

[a] E-1 = Chemscore lipophilic term and fraction of total Van der Waals energy.
[b] E-2 = Hydrophobic reward.
[c] E-3 = Electrostatic reward.
[d] Desolvation penalty term = +2.27 K cal/mol was observed in this case.

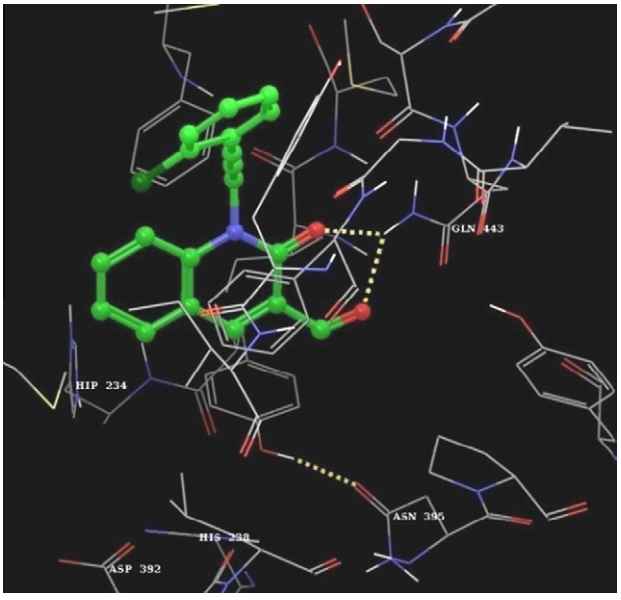


Figure 2. Docking of **4e** at the active site of PDE4B.

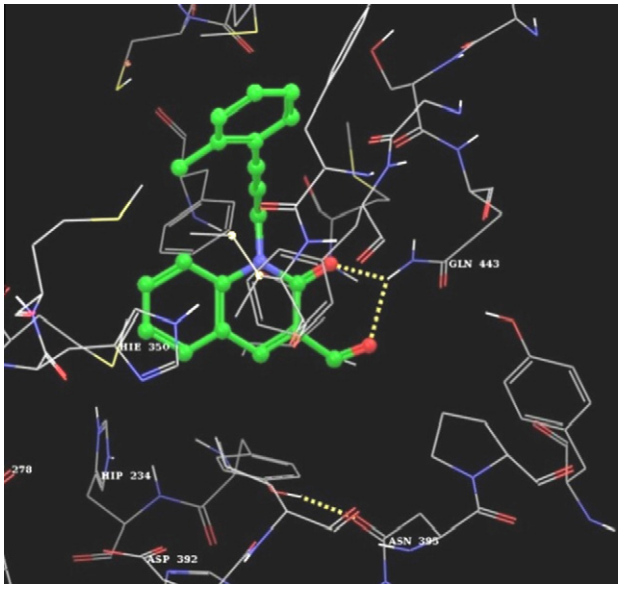


Figure 3. Docking of **4f** at the active site of PDE4B.

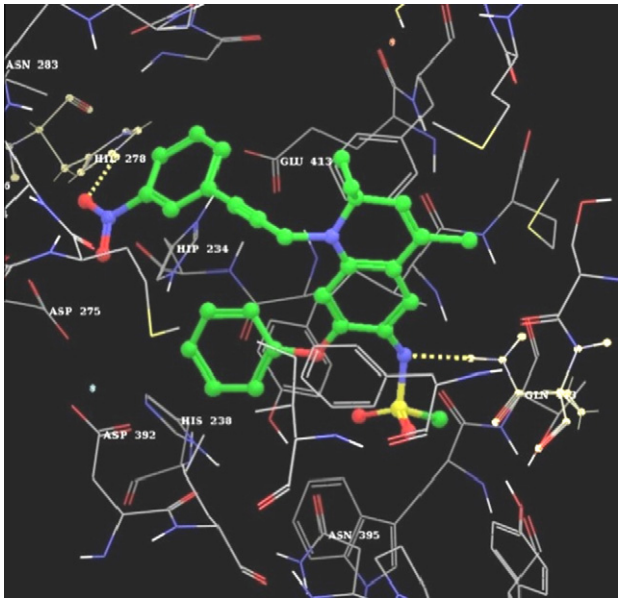


Figure 4. Docking of **7b** at the active site of PDE4B.

entries 7–11). In a dose response study compound **7d** showed inhibitory activities accross all the dose tested (23%, 16%, 11%, and 10% at 10, 3, 1 and 0.3 μM). Moreover, **7d** showed significant inhibition of TNF-α (a marker for many inflammatory disorder)[18], that is, 47% and 35% at 30 and 10 μM, respectively in vitro.

In order to understand the nature of interactions of these molecules with PDE4B docking studies were carried out using the compounds **4e**, **4f**, **7b**, **7c**, and **7d**. The GLIDE scores were obtained after docking of these molecules with PDE4B protein is summarized in Table 2. The data shown in Table 2 clearly suggests that these molecules bind well with PDE4B. H-bonding interaction was observed in the case of **4e** and **4f** involving both-C═O groups of these molecules and the –NH group of the GLN443 residue of the PDE4B protein (Figs. 2 and 3). In case of **7b** H-bonding interaction was observed between the $–NO_2$ oxygen of the molecule with the –NH group of Histidine (HIE278) (Fig. 4). Additionally, the nitrogen of the $NHSO_2CH_3$ moiety interacted with the –NH group of the GLN443 of the PDE4B protein. A combination of both hydrophobic and electrostatic interactions with the active site of the PDE4B protein was observed in case of **7c** (Fig. 5). The Cl group of the chlorobenzene moiety of **7c** showed electrostatic interaction with the –NH group of GLN443 residue of PDE4B protein. The groups participated in the H-bonding interactions between **7d** and PDE4B (Fig. 6) involved –S═O oxygens of the molecule and the ASN283 and GLN284 residues of PDE4B protein. Additionally, the ester oxygen of **7d** interacted with the –NH group of the GLN443 residue of PDE4B protein.

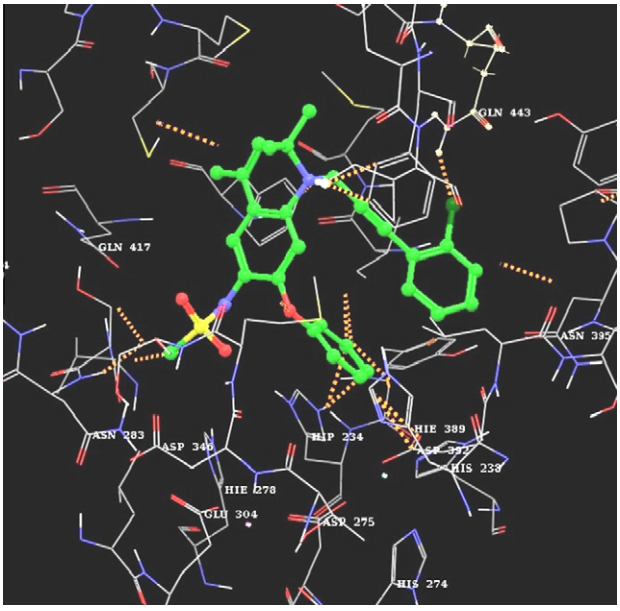


Figure 5. Docking of **7c** at the active site of PDE4B.

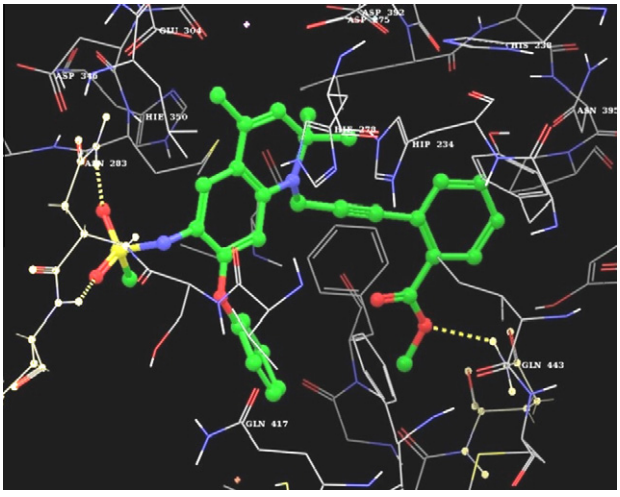


Figure 6. Docking of **7d** at the active site of PDE4B.

In conclusion, for the first time nimesulide based novel 1-alkynyl substutited 1,2-dihydroquinoline derivatives and their 2-oxo analogues have been designed and synthesized. A number of compounds showed PDE4B inhibitory properties in vitro and good interactions with PDE4B protein in silico. The strategy presented here therefore has potential for the discovery of novel PDE4 inhibitors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.08.033.

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