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PII: S0960-894X(16)31295-1
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.12.030
Reference: BMCL 24519

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 16 September 2016
Revised Date: 16 November 2016
Accepted Date: 8 December 2016

Please cite this article as: Mareddy, J., Suresh, N., Ganesh Kumar, C., Kapavarapu, R., Jayasree, A., Pal, S., 1,2,3-Triazole-nimesulide hybrid: Their design, synthesis and evaluation as potential anticancer agents, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.12.030

Graphical Abstract

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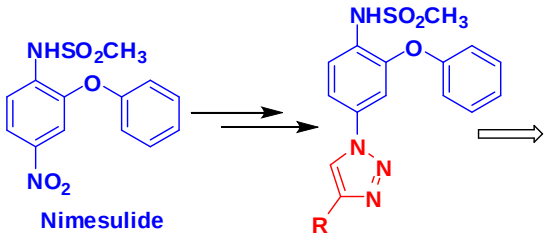
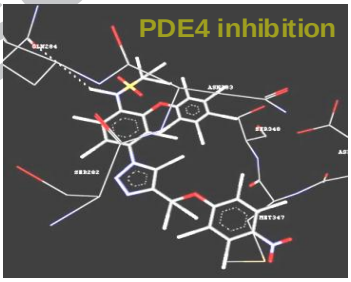


Cytotoxic properties

Compound	IC_{50} (μM) A549 cells
3f	7.1± 0.22
3g	6.7± 0.15
3i	6.6 ± 0.23



Bioorganic & Medicinal Chemistry Letters
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1,2,3-Triazole-nimesulide hybrid: Their design, synthesis and evaluation as potential anticancer agents

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Nimesulide
1,2,3-Triazole
Azide
Alkyne
Anticancer activity

ABSTRACT

A new hybrid template has been designed by integrating the structural features of nimesulide and the 1,2,3-triazole moiety in a single molecular entity at the same time eliminating the problematic nitro group of nimesulide. The template has been used for the generation of a library of molecules as potential anticancer agents. A mild and greener CuAAC approach has been used to synthesize these compounds *via* the reaction of 4-azido derivative of nimesulide and terminal alkynes in water. Three of these compounds showed promising growth inhibition (IC_{50} ~ 6-10 µM) of A549, HepG2, HeLa and DU145 cancer cell lines but no significant effects on HEK293 cell line. They also inhibited PDE4B *in vitro* (60-70% at 10 µM) that was supported by the docking studies (PLP score 87-94) *in silico*.

Nimesulide (**A**, Fig.1),[1] a well known non-steroidal anti-inflammatory drug (NSAID) is an moderately selective inhibitor of cyclooxygenase-2 (COX-2). The enzyme COX-2 is one of the two isoforms of COX that is responsible for the formation of prostanoids, including thromboxane and prostaglandins such as prostacyclin. Nimesulide also exhibited impressive anticancer properties. For example, studies have shown that it played an important role in controlling growth, proliferation and apoptosis of cancer cell lines and tumors.[1] However, its use is associated with an increased risk of hepatotoxicity that resulted withdrawal of this drug from the market in many countries. Studies have indicated that the observed hepatotoxicity of nimesulide can be linked to its protonophoretic and NAD(P)H oxidizing properties caused by its nitro group.[2] Indeed, these effects were suppressed when the nitro group was replaced by an amine[3] or hydroxyl moiety[4] (metabolites **B** and **C**, Fig. 1). Notably, 4-cyano analog of nimesulide (**D**, Fig.1) was synthesized and identified as a potent anti-inflammatory agent when tested in rats.[5] It is therefore desirable to replace the nitro group by an appropriate unsaturated group or substituent without affecting its pharmacological properties and irrespective of its uses as a NSAID or anticancer agent.

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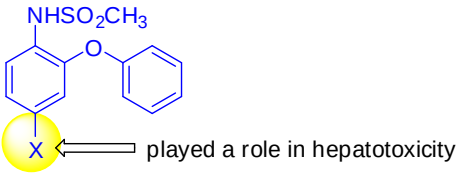


A; X = NO_2
B; X = NH_2
C; X = OH
D; X = CN

Fig. 1. Nimesulide (**A**), its 4-amino and 4-hydroxy metabolite (**B** and **C**) and 4-cyano analog (**D**).

The compounds containing 1,2,3-triazole framework on the other hand have been reported as potential anticancer agents.[6-10] Indeed, the 1,2,3-triazole-dithiocarbamate hybrids (**E**, Fig. 2) have shown moderate to potent activity against human gastric cancer MGC-803 and human breast cancer MCF-7 cell lines.[10] The study has indicated that 1,2,3-triazoles show promising pharmacological properties because of their capability of forming H-bonds thereby improved solubility and ability to interact with biomolecular targets.[11] They are also stable to metabolic degradation compared to the other similar compounds containing three adjacent nitrogen atoms. All these observations and our interest in nimesulide[12] and 1,2,3-triazole derivatives[13-16] prompted us to explore a series of novel 1,2,3-triazole-nimesulide hybrids based on **F** (Fig. 2) as potential anticancer agents. We

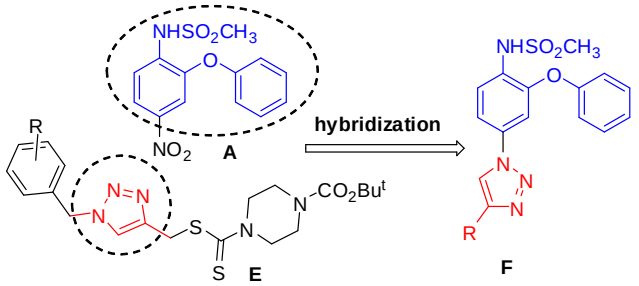
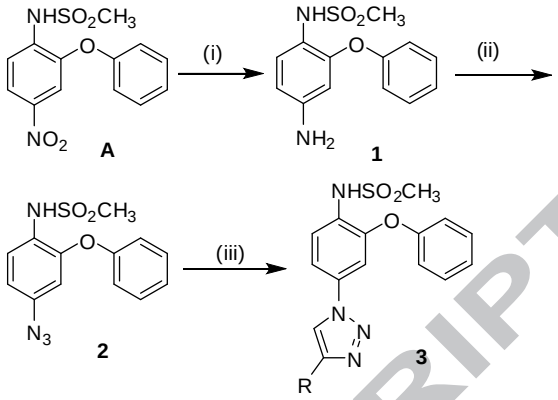


Fig.2. The reported 1,2,3-triazole-dithiocarbamate hybrids (**E**) and the design of 1,2,3-triazole-nimesulide hybrids (**F**).

anticipated that integrating structural features of nimesulide (**A**) and 1,2,3-triazole moiety of **E** in a single molecular entity at the same time eliminating the problematic nitro group of **A** may afford compounds possessing interesting pharmacological properties. Herein we report the preliminary results of this study.

The paradigm of "click chemistry" begun with the seminal discovery of the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) by Meldal and Sharpless's group independently.[17-19] Soon after this most reliable, functional group tolerant and efficient bond-forming reaction became a widespread synthetic transformation that found applications in chemistry, biology, and materials science. Initially the 1,3-dipolar cycloaddition reaction of azides and alkynes was studied by Huisgen and co-workers.[20] The uncatalyzed reaction required the use of high temperature and was found to afford mixtures of 1,4- and 1,5-triazole regioisomers. Later, the CuAAC afforded 1,4-disubstituted 1,2,3-triazoles exclusively and was popularly termed as "click reaction". The reaction generally involves *in situ* generation of the required Cu(I) catalyst *via* the reduction of a Cu(II) salt with Na-ascorbate. A plethora of reaction conditions have been investigated to improve the efficiency and greenness of this process. These include the use of various Cu catalytic systems e.g. Cu with other elements such as Cu(II) / sacrificial reducing agent, Cu(0) / oxidizing agent or Cu(I) / auxiliary ligand, and the use of Cu(I) species alone.[21] The use of various organic solvents and water has also been investigated and found to be effective for click reactions. Nevertheless, maintaining the TAPE (time, atom and pot economy) in the synthesis of library of small molecules or new chemical entities can lead to considerable 'greening' of a synthetic route over conventional synthetic methods. Hence development of such strategies has gain considerable interest both in academia and industrial R & Ds. We now report a CuAAC based strategy for the rapid synthesis of our target molecules based on **F** i.e. **3** (Scheme 1). This strategy involved the use of water as a very efficient and green solvent that accelerated the click reaction by several fold in the present case compared to that performed in an organic solvent.

The necessary azide **2** required for the synthesis of compound **3** was prepared from nimesulide **A** that was reduced[15] to the corresponding amine **1** which on treatment with $NaNO_2$ followed by Na-azide afforded **2** (Scheme 1). The obtained 4-azido analogue of nimesulide was then coupled with a number of terminal alkynes[13,22] in the presence of $CuSO_4$•$5H_2O$ and Na-ascorbate in water at room temperature to afford the desired 1,2,3-triazole-nimesulide hybrids **3**. Notably, the reactions were completed within 5-20 min affording the expected product **3a-r** in good yields. However, a significantly longer reaction time was required to afford the product **3i** that contains an electron withdrawing NO_2 group. Perhaps the reactivity of the corresponding alkyne reactant i.e. *p*-$NO_2C_6H_4OCH_2C{\equiv}CH$ was greatly influenced by the presence of NO_2 group under the reaction condition employed. Nevertheless, we were delighted to observe such a quick reaction rate in majority of the cases without using any additives and/or ligands or microwave or



R = (time, % yield)

3a; Ph (5 min, 95%)

3b; $PhOCH_2$ (15 min, 90%)

3c; $C_{10}H_7OCH_2$ (15 min, 89%)

3d; *p*-$CH_3C_6H_4$ (15 min, 94%)

3e; *p*-$CH_3C_6H_4OCH_2$ (10 min, 95%)

3f; *p*-$ClC_6H_4OCH_2$ (10 min, 97%)

3g; *p*-Cl(*m*-CH_3)$C_6H_3OCH_2$ (15 min, 80%)

3h; *o*-$ClC_6H_4OCH_2$ (10 min, 96%)

3i; *p*-$NO_2C_6H_4OCH_2$ (20 min, 75%)

3j; *p*-CHO(*o*-OCH_3)$C_6H_3OCH_2$ (5 min, 95%)

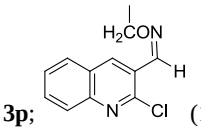
3k; *m*-CHO(*o*-OCH_3)$C_6H_3OCH_2$ (5 min, 79%)

3l; ($C_{10}H_7O_2$)OCH_2 (5 min, 77%)

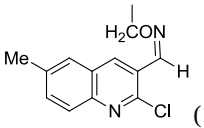
3m; $C_9H_6NOCH_2$ (5 min, 66%)

3n; *p*-CH_2OH(*o*-OCH_3)$C_6H_3OCH_2$ (5 min, 83%)

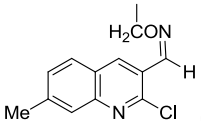
3o; *m*-CH_2OH(*o*-OCH_3)$C_6H_3OCH_2$ (5 min, 86%)



3p; (10 min, 80%)



3q; (10 min, 85%)

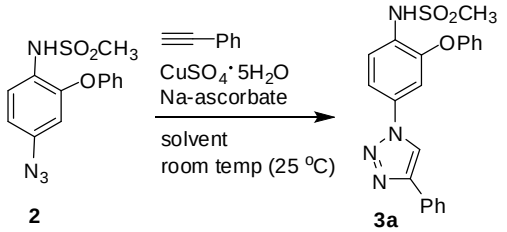


3r; (10 min, 84%)

Scheme 1. Reagents and conditions: (i) Sn/HCl, (ii) $NaNO_2$ / H_2O, 0 °C, NaN_3, 1h, 89%; (iii) R-C≡CH, $CuSO_4$•$5H_2O$, Na-ascorbate, H_2O, room temp.

ultrasound.[23] It is worthy to mention that the reaction progressed well in these cases in spite of moderate to poor solubility / miscibility of reactants in water. In order to assess the effect of water as a solvent in the present coupling reaction we performed a limited study on the reaction of azide **2** with phenyl acetylene using a number of solvents (Table 1). Since PEG (polyethylene glycol) is considered as another green solvent in organic reactions hence we explored its use in the present reaction. Notably, a poor yield of desired compound **3a** was obtained when the reaction was performed in PEG-400 for 5 min (entry 2 vs 1, Table 1) and the reaction did not reach to the completion

Table 1: The effect of solvents on the CuAAC of **2** with phenyl acetylene.[a]



2 **3a**

Entry	solvent	Time (min)	Yield[b] (%)
1.	H_2O	5	95
2.	PEG-400	5	12
3.	PEG-400	180	89
4.	DMF	180	93
5.	MeCN	180	80

[a]Reaction conditions: azide **2** (1 mmol), phenylacetylene (1 mmol), $CuSO_4$•$5H_2O$ (0.25 mmol), sodium ascorbate (0.25 mmol) in a solvent (5 mL) with vigorous stirring.

[b]Isolated yield.

(according to TLC test). However, the reaction was completed when carried out for 180 min affording **3a** in 89% yield (entry 3, Table 1). A similar trend was observed when the reaction was carried out in DMF and MeCN (entry 4 and 5, Table 1). While performing these reactions (in PEG-400, DMF and MeCN) at an elevated temperature (in the range of 50-70 ºC) perhaps could decrease the reaction time without affecting the product yield however, we carried out these reactions at room temperature (25 ºC) in order to maintain the mild nature of the reaction conditions. Nevertheless, it appeared that all the organic solvents tested were found to be inferior to water both in terms of product yield and reaction time. Moreover, water is a green and inexpensive solvent with ample availability in nature.

While the reaction rate enhancement by water was not clear in the present CuAAC of azide **2** with the terminal alkynes however based on the results of studies published earlier[22,24] a probable reaction mechanism is depicted in Scheme S-1 (see the supplementary data file). Being weak base water can function as a proton acceptor and facilitate the deprotonation of the terminal alkyne to give a Cu-acetylide intermediate **I-1** that generates a copper-azide-acetylide complex **I-2**. Being a charged species the formation and solvation / stabilization of **I-2** is expected to be facilitated by water. The complex **I-2** then undergoes cyclization *via* **I-3** followed by protonation *via* **I-4** in the presence of conjugate acid of H_2O. The protonation of **I-4** is also expected to be assisted by water thereby increasing in the reaction rate. This step was much slower in case of PEG-400 thereby increasing the reaction time.

All the synthesized compounds were characterized by spectral (NMR, IR and MS) data. For example ^{1}H NMR spectra of a

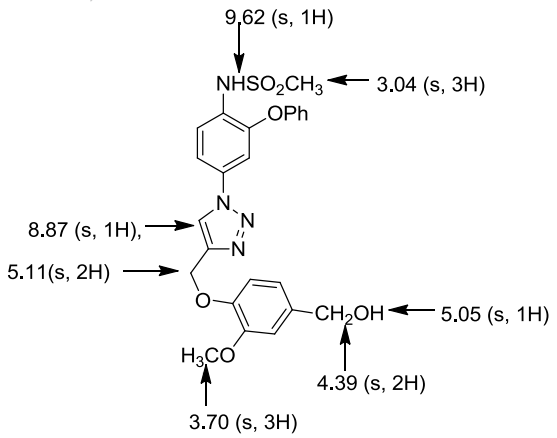
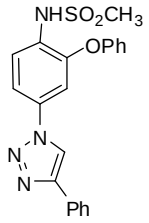


Fig. 3. Representation of partial ^{1}HNMR data of compound **3n**.

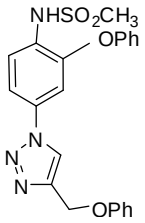
representative compound **3m** (Fig. 3) showed (i) two singlets at δ 5.11 and 4.39 due to two methylene protons, (ii) one singlet at δ 8.87 due to the CH proton of triazole ring, (iii) one singlet at δ 3.70 due to the -OMe protons and (iv) one singlet at δ 3.04 due to the -SO_2Me protons. In the ^{13}C NMR spectra, the OCH_2, OMe and CH_2OH appeared at 63.2, 62.2 and 55.8 ppm respectively whereas -SO_2Me group appeared at δ 41.1 ppm.

Having synthesized a number of 1,2,3-triazole-nimesulide hybrids (**3**) we then decided to assess their cancer cells growth inhibitory properties against various cancer cell lines. We were particularly encouraged by the fact that both nimesulide (**A**) and the triazole derivative **E** (Fig. 2) showed anticancer properties.[1,10] The cancer cell lines used for our study include A549 (lung cancer), HepG2 (liver cancer), HeLa (cervical cancer) and DU145 (prostate cancer). A colorimetric MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay was used to measure the effect of test compounds along with a standard drug doxorubicin as the reference compound. The IC_{50} values for the growth inhibition of cancer cells by compounds **3** and nimesulide[25a,b] (**A**) are presented in Table 2. It is evident from Table 2 that compounds **3f** and **3g** showed good growth inhibition of all the cancer cell lines tested whereas **3c** and **3e** were found to be next best. However the compound **3i** was found to be effective against lung and prostate cancer cell lines. The compound **3b** and **3d** also showed good effects against the prostate cancer cell line. Overall, the compound **3g** and **3i** against lung cancer, compound **3f** against lung cancer, compound **3f** and **3g** against cervical and compound **3f** and **3g** against prostate cancer cell lines were found to be most active in this series. The compound **3h** was found to be the least active in this series. These compounds were also tested against non-cancerous human embryonic kidney cells i.e. HEK293 when none of them showed any significant effects indicating their selectivity towards the growth inhibition of cancer cells. It is worthy to mention that the newly synthesized compounds in general showed improved growth inhibition of cancer cells tested over nimesulide. This could be due to the combined effect of 1,2,3-trizole and the substituent attached to it. While 1,2,3-triazole could be a replacement for -NO_2 group, the substituent attached to it could contribute significantly towards the molecular dispersion force. Thus, to understand their individual role in the observed anti-cancer activities the compound *N*-(4'-fluoro-3-phenoxybiphenyl-4-yl)methanesulfonamide (**4**) prepared *via* the reported method[12] was tested against A549 and HepG2 cell lines and was compared with **3a** and **A**. The observed activities of compound **4** [IC_{50} = 52± 0.41 (A549) and 38.19±0.56 (HepG2)] similar to **A** rather than **3a** indicated important role played by the 1,2,3-triazole moiety in the anticancer activities of **3a**. It may also be noted that the presence of –CH_2O- moiety in **3b-c** and **3e-i** with the exception of **3h** perhaps provided more flexible conformations for these molecules compared to **3a** and **3d** for better molecular interactions as indicated by their activities. Nevertheless, being a new class of cytotoxic agents this series deserved further attention and therefore we focused on elucidating the mechanism of action (e.g. pharmacological target) of this class of compounds. A thorough literature search revealed that nimesulide possess phosphodiesterase type 4 (PDE4) inhibiting property[25c] whereas recent study indicated that PDE4 can be a potential target for cancer.[26] Thus in view of the link between cancer and PDE4 and the reported PDE4 inhibiting properties of nimesulide the most promising compounds i.e. **3f**, **3g** and **3i** were examined *in vitro* at 10 µM using PDE4B enzyme assay[27] along with rolipram[28] as a reference compound. The cAMP specific PDE4 that has four isoforms, e.g., PDE4A-D[29a] is widely expressed in tumor cells. Since PDE4B is the major and most important subtype[29b] among the four subtypes of PDE4 hence this particular subtype was chosen as the target protein initially for *in vitro* and then for docking studies. Indeed, these compounds

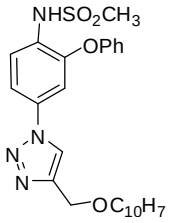
Table 2. The growth inhibition of cancer cells by compounds **3a-i**



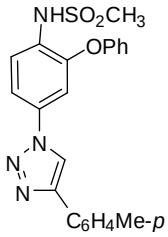
3a



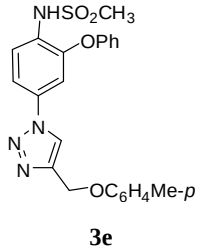
3b



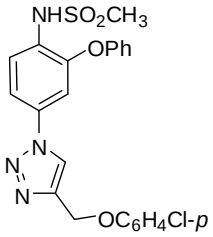
3c



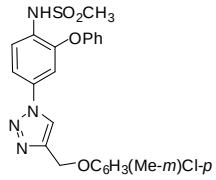
3d



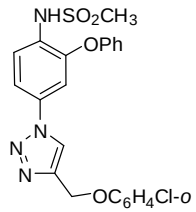
3e



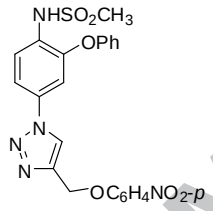
3f



3g



3h



3i

Entry	3	IC_{50} (μM)			
		A549 (lung)	HepG2 (liver)	Hela (cervical)	DU145 (prostate)
1	**3a**	29.9 ± 0.22	13.6 ± 0.21	21.9 ±0.25	14.2 ± 0.16
2	**3b**	n.d.	12.3 ± 0.13	n.d.	10.7 ± 0.11
3	**3c**	8.3 ± 0.26	19.5 ± 0.23	12.8 ± 0.25	9.1±0.23
4	**3d**	n.d.	18.3 ± 0.13	n.d.	11.2± 0.21
5	**3e**	8.0 ± 0.20	13.0 ± 0.11	15.8 ± 0.14	8.2±0.28
6	**3f**	7.1 ± 0.22	7.5 ± 0.09	7.8±0.15	6.4±0.31
7	**3g**	6.7 ± 0.15	9.8 ± 0.12	7.9±0.22	5.9±0.15
8	**3h**	53.8 ± 0.19	25.3 ± 0.13	38.6 ± 0.19	21.1±0.12
9	**3i**	6.6 ± 0.23	n.d.	n.d.	7.2±0.32
10	**A**	67.81± 0.23	35.21±0.72	n.d.	n.d.

A = nimesulide; n.d. = not determined.

showed good inhibition of PDE4 e.g. 62.81 ± 1.20% by **3f**, 67.50 ± 2.07 by **3g** and 70.24 ± 1.60% by **3i** (when rolipram showed 90 ± 4.13 % inhibition). Notably, nimesulide showed 52% inhibition of PDE4 at 10 μM.

To understand the nature of interactions of these compounds with PDE4 we performed docking studies of compound **3f**, **3g**, **3i**, and nimesulide. A known inhibitor of PDE4 e.g. rolipram was used as a reference compound in these studies. The molecular docking simulations were carried out using GRIP method of docking in Biopredicta module of Vlife MDS (Molecular Design Suite) 4.6. The PDE4B protein in complex with rolipram was obtained from Protein Data Bank (PDB ID: 1XMY)[30] and was used as the receptor for this study. The GRIP docking employs PLP (Piecewise Linear Pair wise Potential) scoring function for protein ligand interactions which includes hydrogen bonding, steric interactions, van der Waals interactions, hydrophobic interactions and electrostatic interactions. Accordingly, compounds **3f**, **3i** and **3g** showed better PLP score (docking scores) than nimesulide (Table 3) which is in agreement with the

Table 3. Results of docking studies

Compounds	PLP score	H- bond interactions
3f	-87.42 kcal/mol	GLN417
3g	-92.87 kcal/mol	ASP346
3i	-94.65 kcal/mol	GLN284
Nimesulide	-58.52 kcal/mol	SER442

PLP = Piecewise Linear Pair wise Potential

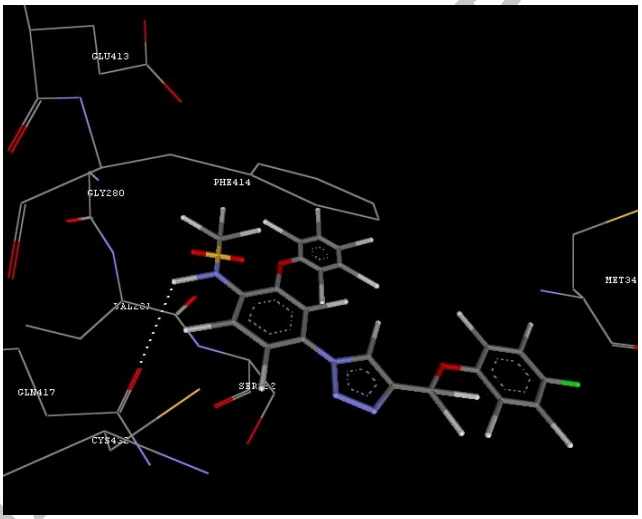


Fig. 4. Docking of compound **3f** into PDE4B (PDB ID: 1XMY).

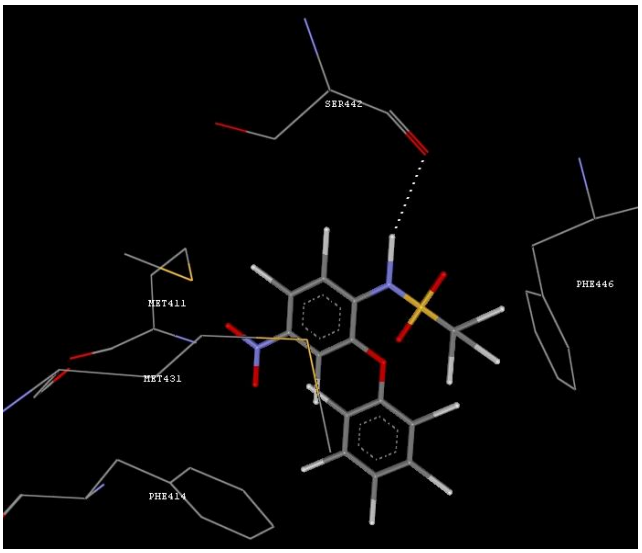


Fig. 5. Docking of nimesulide into PDE4B (PDB ID: 1XMY).

observed %inhibition shown by these compounds. Indeed, all the test compounds showed H-bond interaction through the –NH group of their methanesulphonamide (-$NHSO_2Me$) moiety with good binding modes in the active site of PDE4B on post docking simulations (Fig 4 and 5, see also Fig S-1 and S-2 in supplementary data file). For example, the –NH group of -$NHSO_2Me$ moiety participated in the H-bond interaction with the GLN417 and GLN284 residue of PDE4B, respectively in case of **3f** (Fig 4) and **3i** (Fig. S-2, supplementary data file). Similarly, the –NH group formed H-bond with the ASP346 and SER442 residue of PDE4B in case of **3g** (Fig. S-2, supplementary data file) and nimesulide (Fig 5). Overall, it is evident from this study that the cancer cells growth inhibitory properties shown by these compounds against various cancer cell lines could be due to their inhibition of PDE4.[31]

In conclusion, a new hybrid template has been designed by integrating the structural features of nimesulide and the 1,2,3-

triazole moiety in a single molecular entity at the same time eliminating the problematic nitro group of nimesulide. The template has been used for the generation of a library of molecules as potential anticancer agents. A mild and greener approach has been used to synthesize these compounds in good yields. The methodology involved a CuAAC between 4-azido derivative of nimesulide and readily available terminal alkynes in the presence of precatalyst $CuSO_4$•$5H_2O$ and sodium ascorbate. This reaction was performed in water at ambient temperature as the study indicated that water was not only a green solvent for this transformation but also superior to other organic solvents in terms of reaction time and product yields. All the synthesized 1,2,3-triazole-nimesulide hybrids were tested for their cancer cells growth inhibitory properties against various cancer cell lines including A549 (lung cancer), HepG2 (liver cancer), HeLa (cervical cancer) and DU145 (prostate cancer). The compounds **3f**, **3g** and **3i** were found to be best among all the compounds tested. They also inhibited PDE4B *in vitro* that was supported by the results of *in silico* docking studies. Overall, the new template described here could be useful for the identification of novel and potential anticancer agents. Moreover, being faster and eco friendly the methodology described here may find wide applications in building library of small molecules related to this new framework.

Acknowledgements

The authors (J. M. and S. P.) thank Mr. M. N. Raju, the chairman of MNR Educational Trust for constant support and encouragement.

Supplementary data

Supplementary data associated with this article can be found, in the on line version, at xxxxxxxxx

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