© 2018 IJSRST | Volume 4 | Issue 10 | Print ISSN : 2395-6011 | Online ISSN : 2395-602X
Themed Section: Science and Technology

Development of Newer Bioactive Triazolopyrimidines

Jayanti S. Rajora*[1]
*[1]Department of Chemistry, Government Science Collge-Gandhinagar, Gujarat, India
jaya.rajora@gmail.com[1]

ABSTRACT

Main objective of this paper is to determine the modulus of elasticity of fibre reinforced concrete with the addition of bottom ash .And also to determine the strength of concrete by using polyolefin and steel fibres. Pyrimidine derivatives have been of enormous interest due to their wide spectrum biological activity profile. Among pyrimidine derivatives, triazolopyrimidines have attracted significant attention from the bioactivity point of view.

The present paper covers a brief report of approaches to newer bioactive triazolopyrimidine derivatives.

Keywords: Pyrimidines, Triazolopyrimidines, Biological Activity

I. INTRODUCTION

Triazolopyrimidines have drawn much more attention of organic chemists for the development of related compounds in the medicinal field because of their structural similarity to the adenine and purine bases.

Development of new triazolopyrimidine structures has been of considerable interest due to their medicinal importance.

The combination of a pyrimidine nucleus with triazolo ring to form triazolopyrimidine systems possibly take place in four non-identical modes, which lead to the formation of isomeric structures, and all of the isomers possess a nitrogen bridgehead. These four isomers are: 1,2,4-triazolo[1,5-*a*]pyrimidine; 1,2,4-triazolo[1,5-*c*]pyrimidine; 1,2,4-triazolo[4,3-*a*]pyrimidine; 1,2,4-triazolo[4,3-*c*]pyrimidine.

Several literature reports have described the preparation and biological evaluation of newer triazolopyrimidine derivatives [1, 2].

The present paper reports brief overview of approaches to development of newer triazolopyrimidines and their bioactivity profile.

II. ADVANCES IN THE DEVELOPMENT OF TRIAZOLOPYRIMIDINES

David, W. P. et al. have reported the structural modification of a previously known hit compound to design a potential traizolopyrimidine based antagonists of chemokine receptor [3].

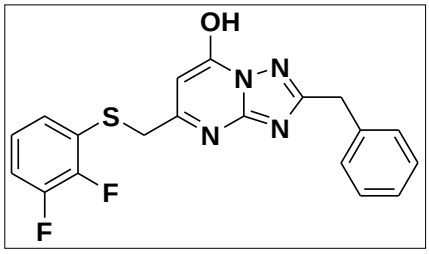
The triazolopyrimidine derivatives were optimized by introduction of various substituents at the different positions.

The derivatives were then screened for their inhibition potential for chemokine receptor. The structure activity relationship was determined for introduction and alteration of various structural features.

It was revealed that introduction of the triazolopyrimidine core enhanced the inhibition potential remarkably as compared to the hit compound.

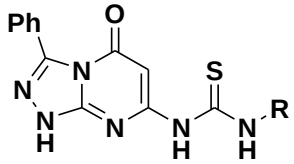
Also, the structural optimization resulted in better pharmacokinetic properties and made the derivatives orally available. The structurally optimized triazolopyrimidines possessed better drug-like properties.

One compound from the series bearing difluoroaryl modification displayed the highest antagonist potential. It also had less toxicity and good bioavailability profile.



Ameen, A. A. et. al. have reported design, preparation and characterization of novel diversely substituted triazolopyrimidines [4]. The triazolopyrimidines were designed to have novel substitutions viz. imine, imide and thioamide functionalities.

The newly developed triazolopyrimidines were screened for their antibacterial and antifungal activities. Five compounds from the series displayed superior antibacterial and antifungal activities as compared to the reference drugs.



Triazolopyrimidines as novel carbonic anhydrase (CA) inhibitors were reported [5]. They have given the design and synthesis of new set of triazolopyrimidine based arylsulphonamides, which were evaluated for their potential to inhibit different forms of CA.

The newly developed triazolopyrimidne based arylsulphonamides displayed good inhibition potential.

Further, these compounds showed selective inhibition of CA form IX at very low concentrations of nanomolar level.

Further, the docking studies were performed which displayed positive binding profile for the CA IX and X.

Chao-Nan, C. et al. have reported design and preparation of novel sulphonamide derivatives of triazolopyrimidine as AHAS inhibitors [6]. The derivatives were prepared by structural modification of known herbicide Flumetsulm.

The newly developed trizolopyrimidines contained alkoxy group as replacement of alkyl group of the Flumetsulm.

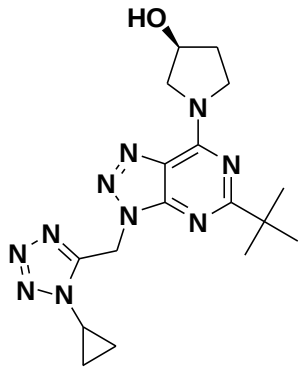
However, it was revealed that the new trizolopyrimidine derivative displayed less inhibition potential as compared to Flumetsulm. They performed various computational and binding profile studies and explained the reason behind the decline in the inhibition potential in vitro.

On the contrary, the new triazolopyrimidine derivative displayed equivalent activity to Flumetsulm in vivo. The half-life of the new triazolopyrimidine derivative was lessened as compared to Flumetsulm.

Matthias, N. et al. have designed, synthesized and evaluated series of novel triazolopyrimidine compounds as agonists of CB receptor [7]. The novel triazolopyrimidine derivatives were designed from the structural modification of a previously reported lead compound.

The newly developed triazolopyrimidines showed good potential as agonists. The newly developed triazolopyrimidines had better solubility and lipophilic profile as compared to the lead compound.

The active compounds were further tested in different models to assess their CB agonism in order to reduce inflammation response in the kidney. One compound from the series showed good reduction in the inflammation response and also had desired oral availability.



Chao-Nan, C. et al. have reported design, preparation and biological evaluation of new triazolopyrimidines as herbicides [8]. The sulphonamide group bearing triazolopyrimidines were tested for their potential for the inhibition of acetolactate synthase.

The sulphonamide bearing triazolopyrimidines displayed good inhibition against AHAS of Mouse-ear cress. Few compounds displayed superior activity as compared to the reference herbicide.

Further, studies by simulation showed that the carboxylate group displayed binding with the AHAS. One compound from the series particularly displayed wide spectrum activity in different assays.

Probir et. al. has performed the docking and quantitative structure–activity relationship studies on previously reported triazolopyrimidine having the inhibition potential against DHODH [9].

The quantitative structure activity relationships studies gave insights about different descriptors and properties relevant to activity of the compound.

Further, binding profile of the compound with the enzyme was evaluated by the docking studies. It was revealed that the triazolopyrimidine bearing 2-alkyl group was binding with the aminocarboxylic acid part and the aryl substitutent was binding with the lipophilic part of the enzyme.

It was concluded based on the quantitative structure–activity relationship studies that newly developed triazolopyrimidine compounds can serve as the potential candidates for further developments in the therapeutic area.

Fei, Y. et al. The triazolopyrimidines were screened for their anti-viral activity [10].

These triazolopyrimidines were particularly tested for their inhibition potential of HIV-1 Tat–TAR using three different assays. The compounds displayed good inhibition in all the three assays.

Further, docking studies were performed to assess the binding modes of the compounds. The findings of this study confirmed the experimental activity findings.

Said, A. S. et al. have reported design, preparation and characterization of novel triazolopyrimidine derivatives and screened for their antiepileptic, analgesic and anti-inflammatory potential [11].

The newly developed triazolopyrimidine derivatives showed good anti-inflammatory activity. Some of the compounds showed superior anti-inflammatory action as compared to three standard drugs.

Also, the compounds had lower toxicity as compared to the standard drugs. Few compounds from the series displayed good inhibition of cyclooxygenase.

Few compounds from the series displayed triple action as in anti-epileptic, analgesic and anti-inflammatory activities which was superior than the used standard drugs.

Margaret, A. P. et al. have reported design, preparation, characterization and anti-malarial activity of novel triazolopyrimidine derivatives [12]. The triazolopyrimidine derivatives were specifically screened for their ability to inhibit DHODH of P. falciparum preferably over the enzyme present in human cells.

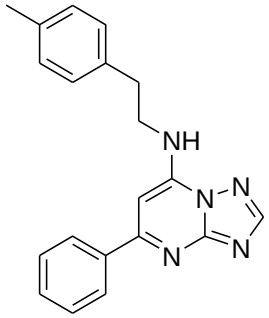
The newly developed triazolopyrimidine were screened for the inhibition potential through high-throughput screening method.

One compound from the series displayed excellent inhibition potential at nano-molar concentration as well as preferable inhibition of DHODH of P. falciparum over the human enzyme.

Edison, S. Z. et al. have explored systematic study of triazolopyrimidine derivatives antimycobacterial activity [13]. They have synthesized di-substituted triazolopyrimidines and screened them against M. tuberculosis.

They have established structural activity relationships in which they identified the essential features for the activity from all the segments of the scaffolds individually.

It was observed that presence of aryl ring at the carbon no. 5 and ethyl-chain as the connecting group at the carbon no. 7 were essential for good activity. Further, they also assessed their susceptibility to biotransformation and it was concluded that compounds were stable metabolically.



Design and preparation of a prospective of new class of triazolopyrimidines containing pyrimidinyl fragment as inhibitors of acetylcholinesterase have been reported [14].

The newly developed triazolopyrimidines were assessed for their inhibition potential in vitro and their activity was compared to the reference drug Donepezil. Three compounds from the series showed good inhibition potential with the low IC_{50} value.

Among them, one compound showed inhibition comparable to the reference drug. Virtual molecular simulation studies were also performed for the most active compound which confirmed the findings of the in vitro screening. The most active compound also did not display any toxicity.

Sobhi, M. G. et al. have reported design, synthesis and characterization of novel bis-triazolopyrimidines [15]. The bis-traizolopyrimidine derivatives were prepared by the reaction of bis-thione derivative with hydrazonoyl halides.

The structure-elucidation of the newly synthesized compounds was carried out using different spectroscopic methods. The new bis-triazolopyrimidines present an interesting prospect for assessment of medicinal profile.

The synthesis and anticancer evaluation of some new fused triazolopyrimidine derivatives have been reported by Ghada, S. H. et al. [16]. The compounds were screened for their anticancer activity using DNA-binding assay and other in vitro assays.

These compounds were also tested in mice model. Structure activity relationships for triazolopyrimidines were established from the results of these assays and essential structural features for the anticancer activity were determined.

It was concluded that presence of electron-attracting substituents increased the anticancer potential in general. Further, morpholinyl and azophenyl fragments were found to be enhancing the activity.

A new series of di- and tri-substituted triazolopyrimidines containing triazine ring have been designed and synthesized [17]. The triazine and the core scaffolds were joined using the piperazinyl group.

The new trizolopyrimidines were screened for their inhibition potential against the cholinesterase. Out of the seventeen di- and tri-substituted triazolopyrimidines, nine compounds displayed good inhibition potential.

Further, structure activity relationships were established and it was observed that di-substituted triazolopyrimidine derivatives exhibited higher inhibition potential in general as compared to the tri-substituted triazolopyrimidines.

Two compounds from the series displayed highest inhibition potential with very low IC_{50} values less than 1 μM. Also, the most active compounds displayed twenty-eight times higher selectivity for

acetyl-ChE. Pharmacokinetics studies showed that compounds had higher degree of drug-likeness and ocking studies also confirmed the experimental findings.

Margaret, A. P. et al. have reported the structural alteration of the previously reported triazolopyrimidine core bearing lead compound to develop better anti-malarial agents [18].

The arylamine moiety of the lead compounds was replaced with other functional groups and the resulting analogues were studied for their anti-malarial activity.

The newly developed triazolopyrimidine derivatives were screened for their anti-malarial activity. One compound from the series was found to be highly active and was also found to be having better solubility as well as oral bioavailability than the lead compound.

Further, the most active compound also displayed better efficiency in mice model for anti-malarial activity against the P. falciparum.

Also, the compound showed good activity against P. vivax as well. The compound can be a promising target for the development of new anti-malarial agents.

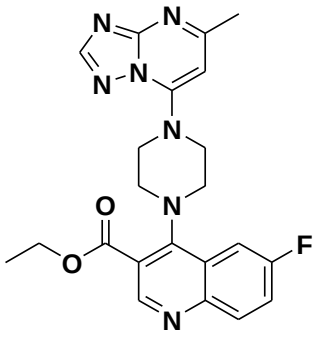
Jitendra, K. et al. have designed, synthesized and evaluated a series of triazolopyrimidine derivatives bearing quinoline scaffold as inhibitors of AChE and BuChE [19].

An efficient synthetic protocol to access diversely substituted triazolopyrimidines bearing quinoline scaffold was developed.

The newly synthesized triazolopyrimidines were screened for their inhibition potential against cholinesterases.

The screening results revealed that while most of the compounds showed moderate to good inhibition of AChE but they were not equally active against BuchE.

Three of the compounds displayed promising activities against AChE at very low concentrations. One compound showed good inhibition potential towards BuChE with twelve times more selectivity as compared to AChE.



Sreekanth, K. et al. have reported novel triazolopyrimidine derivatives as potent inhibitors of DHODH [20]. The novel triazolopyrimidines were prepared by replacement of amine functional group from the previously reported active lead compound with the substituted-naphthyl or aminoindane groups.

The structurally modified triazolopyrimidines were screened for their potential to inhibit DHODH in order to develop better anti-malarial agents.

The results revealed that the replacement proved to be enhancing inhibition potential and selectivity of all compounds. Structure-activity relationships indicated that substituted-naphthyl group bearing derivatives showed higher inhibition as compared to the other groups bearing derivatives.

The compounds were also screened in various models in mice and it was revealed that chloro substituted triazolopyrimidine derivatives had better oral efficiency.

Asier et al. have reported design, preparation and characterization of novel substituted-aryl containing triazolopyrimidines [21]. The compounds were evaluated for their capability to inhibit replication of the virus responsible for the disease of Chikungunya. The compounds displayed selectivity of the inhibition for the virus.

These new triazolopyrimidines were structurally modified at the position no. three of the aryl ring. The structurally optimized triazolopyrimidines were

screened for inhibitory activity in different cells and cell-systems.

The compounds displayed promising inhibition potential with the low IC_{50} value with the micromolar concentration. Further, *in silico* pharmacokinetics was studied for the active compounds and their drug-likeness was determined by assessing various relevant parameters experimentally.

III. ADVANCES IN DEVELOPMENT OF FUSED TRIAZOLOPYRIMIDINES

Mehdi et al. have reported design, preparation and characterization of novel fused triazolopyrimidines [22]. The novel triazolopyrimidine derivatives were furnished by the reaction of pyrimidooxadiazines with hydrazinhydrate followed by treatment with different orthoformates in presence of ethanoic acid.

The developed fused triazolopyrimidines were screened for their anticancer potential against three different cancer cell lines.

Two compounds from the series were further screened for antiproliferative activity. The compounds can be important lead structure for the further structural modification and bioevaluation for the development of newer anticancer agents.

Fakher et al. have reported design, synthesis and characterization of some novel derivatives of pyrano- fused triazolopyrimidines [23]. The preparation was accomplished by the reaction between alkoxymethyleneaminopyran derivatives with hydrazinoamide derivatives.

The structure elucidation was performed by elemental analysis as well as by different spectroscopic techniques.

The newly developed triazolopyrimidines were tested for anti-mutagenicity in PQ 37strain of *E. coli*. The study of structure-activity relationships suggested that clear correlation between the antimutgenic acitivity and functional groups present on the triazolopyrimidine core could not be established.

Takashi et al. have reported simple and facile preparation method for synthesis of fused triazolopyrimidine derivatives [24]. The preparation was accomplished by the reaction of acetylhydrazine derivatives and carboximidates. The preparation protocol was mild and furnished tricylic triazolopyrimidines in high yield and purity.

The newly developed triazolopyrimidines were screened for their antagonist potential against the A_3-type adenosine receptor. The fused tricylic triaozlopyrimidine derivatives displayed good antagonist activity and showed superior selectivity for the human A_3-type receptor.

IV.CONCLUSION

Newer diversely functionalized triazolopyrimidine derivatives have exhibited excellent and wide spectrum bioactivity profile. The potent compounds can be considered as promising lead structures for further drug development and research.

V. REFERENCES

[1] (a) Shaban, M., & Morgaan, A. (1999). The Chemistry of 1,2,4-Triazolopyrimidines I: 1,2,4-Triazolo[4,3-a]Pyrimidines, Advances in Heterocyclic Chemistry, 73, 131-176, (b) Shaban, M., & Morgaan, A. (1999). The Chemistry of 1,2,4-Triazolopyrimidines I: 1,2,4-Triazolo[4,3-c]Pyrimidines, Advances in Heterocyclic Chemistry, 75, 243-281.

[2] Shaban, M., & Morgaan, A. (2000). Chemistry of 1,2,4-triazolopyrimidines III: 1,2,4-triazolo[1,5-c]pyrimidines. Advances in Heterocyclic Chemistry, 77. 345-394.

[3] David, W. P., Michelle, B., Zarin, B., Riccardo, C., Steven, C., Brian, C., Peter, H., David, K., Sarah, L., O'Connor, D., John, R., Carsten, S., Lauren, T., Simon, J. W., Roland, W. and Neil,

J. P. (2014). The discovery of potent, orally bioavailable pyrazolo and triazolopyrimidine CXCR2 receptor antagonists. Bioorganic & Medicinal Chemistry Letters, 24: 72-76.

[4] Ameen, A. A., Hoda, A. R. and Khadeja, M. A. (2017). Synthesis of novel 1, 2, 4-triazolopyrimidines and their evaluation as antimicrobial agents, Medicinal Chemistry Research, 26: 120-130.

[5] Mohamed, A. M., Al-Qalawi, H. R., El-Sayed, W. A., Arafa, W. A., Alhumaimess, M. S. and Hassan, A. K. (2015). Anticancer activity of newly synthesized triazolopyrimidine derivatives and their nucleoside analogs. Acta Poloniae Pharmaceutica, 72(2): 307-18.

[6] Chao-Nan, C., Li, L., Feng-Qin, J., Qiong, C., Hui, X., Cong-Wei, N., Zhen, X., Guang-Fu, Y. (2009). Design and synthesis of N-2,6-difluorophenyl-5-methoxyl-1,2,4-triazolo[1,5-a]-pyrimidine-2-sulfonamide as acetohydroxyacid synthase inhibitor. Bioorganic & Medicinal Chemistry, 17: 3011-3017.

[7] Matthias, N., Jean-Michel, A., Stefanie, B., Catarina, B., Jìrgen, F., Uwe, G., Sabine, G., Stephan, R., Benno, R., Sebastien, S., Franz, S., Tanja S. G. and Christoph U. (2016). Novel triazolopyrimidine-derived cannabinoid receptor 2 agonists as potential treatment for inflammatory kidney diseases. ChemMedChem, 11: 179-189.

[8] Chao-Nan, C., Qiong, C., Yu-Chao, L., Xiao-Lei, Z., Cong-Wei, N., Zhen, X. and Guang-Fu, Y. (2010). Syntheses and herbicidal activity of new triazolopyrimidine-2-sulfonamides as acetohydroxyacid synthase inhibitor. Bioorganic & Medicinal Chemistry, 18: 4897-4904.

[9] Probir, K. O. and Kunal, R. (2010). Chemometric modeling, docking and in silico design of triazolopyrimidine-based dihydroorotate dehydrogenase inhibitors as antimalarials. European Journal of Medicinal Chemistry, 45: 4645-4656.

[10] Fei, Y., Ruifang, P., Dekai, Y., Meizi, H., Chunlei, Z., Shuguang, C. and Ming, Y. (2010). Design, synthesis, and biological evaluation of novel substituted [1,2,3]triazolo[4,5-d]pyrimidinesas HIV-1 Tat–TAR interaction inhibitors. Pure and Applied Chemistry, 82: 339-347.

[11] Said, A. S., Nermien, M. S. and Mohamed, M. A. (2009). Analgesic, anticonvulsant and anti-inflammatory activities of some synthesized benzodiazipine, triazolopyrimidine and bis-imide derivatives. European Journal of Medicinal Chemistry, 44: 4787-4792.

[12] Margaret, A. P., Ramesh, G., Nicholas, A. M., John, W., Farah, E. M., Jeffrey, B. and Pradipsinh, K. R. (2008). Triazolopyrimidine-based dihydroorotate dehydrogenase inhibitors with potent and selective activity against the malaria parasite. *Plasmodium falciparum*. Journal of Medicinal Chemistry, 51: 3649-3653.

[13] Edison, S. Z., Aaron, K., Steven, M., Erik, J. H., Paul, L. O., Guillermo, C., Kallolmay, B., Naresh, K., Jeffrey, C., Thierry, M., Philip, A. H., Joshua O. and Tanya P. (2017). The synthesis and evaluation of triazolopyrimidines as anti-tubercular agents. Bioorganic & Medicinal Chemistry, 25: 3922-3946.

[14] Jitendra, K., Asim, G., Marziya, S., Anju, S., Ashutosh, S., Ehtesham, J., Nitin, S., Nirotpal, M., Nasimul, H. and Jayaram, B. (2018). Pyrimidine-Triazolopyrimidine and Pyrimidine-Pyridine Hybrids as Potential Acetylcholinesterase Inhibitors for Alzheimer's Disease. ChemistrySelect, 3: 736 – 747.

[15] Sobhi, M. G., Thoraya, A. F., Eman, M. H. and Nadia, T. A. (2018). Terephthalaldehyde: An effecient key precursor for novel synthesis of

some interesting bis-thiazoles and bis-triazolopyrimidinones. Journal of Heterocyclic Chemistry, 55: 750-755.

[16] Ghada, S. H., Magda, A. E., Mahmoud, B. E., Said, M. B., Azza, R. M., Farid, A. B. (2017). Synthesis and antitumor testing of certain new fused triazolopyrimidine and triazoloquinazoline derivatives. Arabian Journal of Chemistry, 10: S1345-S1355.

[17] Ehtesham, J., Poonam, M., Mudasir, M., Jitendra, K., Waqar, A., Syed, M., Manisha, T., Nasimul, H. and Jayaram B. (2017). Rational design, synthesis and biological screening of triazine-triazolopyrimidine hybrids as multitarget anti-Alzheimer agents. European Journal of Medicinal Chemistry, 136: 36-51.

[18] Margaret, A. P., Karen, L. W., Sreekanth, K., Xiaoyi, D., John, W., David, W., Michael, J. P., Pradipsinh, K. R. and Susan, A. C. (2016). A triazolopyrimidine-based dihydroorotate dehydrogenase inhibitor with improved drug-like properties for treatment and prevention of malaria. ACS Infectious Diseases, 2: 945-957.

[19] Jitendra, K., Poonam, M., Anju, S., Ehtesham, J., Mudasir, M., Mohammad, M., Ashutosh, S., Manisha, T., Nasimul, H. and Jayaram B. (2016). Synthesis and screening of triazolopyrimidine scaffold as multifunctional agents for Alzheimer's disease therapies. European Journal of Medicinal Chemistry, 119: 260-277.

[20] Sreekanth, K., Xiaoyi, D., Karen, L. W., Jose, M. C., Maria, M., John, W., Farah, E. M., Diana, R. T., Krishne, M., Kakali, R. R., Gong, C., Santiago, F. B., Iñigo, A. B., David, W., Susan, A. C., and Pradipsinh K. R. (2016). Tetrahydro-2-naphthyl and 2-indanyl triazolopyrimidines targeting plasmodium falciparum dihydroorotate dehydrogenase display potent and selective antimalarial activity. Journal of Medicinal Chemistry, 59: 5416-5431.

[21] Asier, G., Ana, M., Leen, D., Alfonso P., Siti, N. A., Rana, A., Pieter, L., Lisa, F. P., Gilles, Q., Johan, N. and María, P. (2018). Inhibition of the replication of different strains of chikungunya virus by 3-aryl-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones. ACS Infectious Diseases, 4: 605-619.

[22] Mehdi, B., Mohammad, R., Ali, S., Marzieh, A, Hoda, A. –M. and Mohsen N. (2011). Synthesis of new derivatives of 3-aryl-1,5-dimethyl-1h-[1,2,4]triazolo[40,30:1,2]pyrimido[4,5-e][1,3,4]oxadiazines as potential antiproliferative agents, Journal of Heterocyclic Chemistry, 48: 183-186.

[23] Fakher, C., Mehdi, M., Hédi, B. M., Leila, C. – G. and Mansour S. (2007). Synthesis and antigenotoxic activity of some naphtho[2,1-b]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives, European Journal of Medicinal Chemistry, 42: 715-718.

[24] Takashi, O., Yasuhisa, K., Kinji, H., Hiroshi, N. and Yoshimitsu N. (2004). Facile synthesis of fused 1,2,4-triazolo[1,5-c]pyrimidine derivatives as human adenosine A3 receptor ligands, Bioorganic & Medicinal Chemistry Letters, 14: 2443-2446.

Cite this Article

Jayanti S. Rajora, "Development of Newer Bioactive Triazolopyrimidines ", International Journal of Scientific Research in Science and Technology (IJSRST), Online ISSN : 2395-602X, Print ISSN : 2395-6011, Volume 4 Issue 10, pp. 599-606, September-October 2018.

Journal URL : https://ijsrst.com/IJSRST2310158