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NOVEL SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED 3, 4-DIHYDROPYRIMIDIN-2 (1H) – ONE (DHPM) DERIVATIVES AND THEIR ANTIBACTERIAL ACTIVITIES

Sambhaji R. Mane*[1], Balaji J. Walekar[1], Anil K. Salunkhe[1], Laxman S. Walekar[2], Popatrao N. Bhosale[3]

*[1]Department of Chemistry, Organic Research Laboratory, Smt. Kusumtai Rajarambapu Patil Kanya Mahavidyalya, Islampur-415 409, Maharashtra, India.

[2]Department of Chemistry, Fluorescence Spectroscopy Research Laboratory, Shivaji University, Kolhapur, Maharashtra, India.

[3]Department of Chemistry, Materials Research Laboratory, Shivaji University, Kolhapur, Maharashtra, India.

ABSTRACT

Recently great attention has been diverted towards cyclic and acyclic nitrogen containing heterocyclic compounds in pharmaceuticals as well as for medicinal purposes. In the present work the desired substituted 3, 4- dihydropyrimidin-2 (1H) - one (DHPM) derivatives were synthesized by treating substituted aromatic aldehydes, urea and ethyl acetoacetate in (1:1:1) mole ratio in presence of Gold nano particles (AuNPs) having size of 15 nm as a catalyst. The structures of newly synthesized derivatives have been established on the basis of their melting points, FT-IR, and ^{1}HNMR spectral analysis. All newly synthesized 3, 4-dihydropyrimidin-2 (1H) - one (DHPM) derivatives were tested for their antibacterial activities using cup plate method by measuring inhibition zone. The B-3 derivative showed more potent antibacterial activity than standard drug Streptomycin.

KEYWORDS

Antibacterial activities, DHPM derivatives, Gold nanoparticles, Inhibition zone and FT-IR.

Author of correspondence:
Sambhaji R. Mane,
Department of Chemistry,
Smt. Kusumtai Rajarambapu Patil Kanya,
Mahavidyalaya, Islampur, Tal - Walwa Dist,
Sangli-415409, Maharashtra, India.

Email: sambhaji_mane@rediffmail.com

INTRODUCTION

N-based heterocyclic compounds are very abundant in nature since they are present as structural subunits in many natural products such as vitamins, hormones and alkaloids. These compounds are also interesting from an industrial point of view especially for the synthesis of pharmaceuticals, herbicides, pesticides, dyes etc[1-6]. The nitrogen containing heterocyclic compounds are a large family of compounds of natural as well as synthetic compounds and mainly used for insecticidal,

analgesic, antibacterial, anticancer, antifungal activities. Recently C. Oliver Kappe was synthesized series of cyclic and acyclic systems close to the 3, 4-dihydropyrimidin-2 (1H) – one (DHPM) which are used as biocidal reagent. Such compounds also have been used as complexing agents. The great electrophilicity of nitrogen atom compared to that of sulfur atom makes the latter more acidic and an active centre in the nucleophilic attack. Multicomponent reactions (MCRs) can provide products with diversity needed in the discovery of new compounds using simple and non hazardous process[7-9]. One such MCR that belongs in the synthesis of 3, 4- dihydropyrimidin-2 (1H) – one (DHPM) derivatives by one pot synthesis. Italian Chemist Pietro Biginelli reported on the acid catalyzed cyclocondensation reaction of ethylacetoacetate, benzaldehyde, and urea[10-14]. Looking at the biological significance of 3, 4-dihydropyrimidin-2 (1H) – one (DHPM) derivatives it was thought to design and synthesize new DHPM derivatives and screen them for their antibacterial activities.

EXPERIMENTAL

Materials and Methods

All chemicals and solvents were used of analytical grade (AR) quality. Most of the chemicals were purchased from Loba Chemie (Mumbai), aldehydes were provided by Merck (Mumbai). Gold nanoparticles (AuNPs) have been synthesized in laboratory. Urea was purchased from PCL (Mumbai). Deionized water was used throughout the experiments.

An efficient synthesis of 3, 4- dihydropyrimidin-2 (1H) -one derivatives done by using Gold (Au) nanoparticles as a catalyst. The Gold (Au) nanoparticles having size of 15 nm becomes an effective catalyst for cyclization. This catalyst is not only applicable to open chained 1, 3 dicarbonyl compounds but also to 1, 3 cyclic 1, 3 open chained compounds. The general reaction for synthesis of DHPM derivatives have been shown in Figure No.1.

In 50 ml two necked round bottom flask, the facile preparation of DHPM derivatives was done by using one pot condensation of aromatic aldehydes , ethyl acetoacetate and urea in 1:1:1 mole ratio using 0.005 gms Gold nanoparticles (AuNPs) and 3 ml Conc. HCl in ethanol as a solvent. This reaction mixture was refluxed for 20-60 min. at 78 ^{0}C temperature. After that reaction mixture was cooled and neutralized with 10% NaOH solution. Then filtered, washed with deionised water and recrystalised in ethanol.

Table No.1 shows the appropriate reaction conditions and yield of DHPM derivatives for different aromatic aldehydes.

RESULTS AND DISCUSSION

DHPM derivatives (B-1 to B-5) were synthesized by one pot multi component reaction. The product purity was confirmed by TLC. The structures of newly synthesized compounds have been confirmed on the basis of spectral FT-IR and ^{1}HNMR data.

FT-IR

The synthesized DHPM derivatives have been characterized by FT-IR spectral analysis. Figure No.2 shows that the spectral analysis of B-1 derivative. The band at around 1182 cm^{-1}, 1237 cm^{-1}, 1700 cm^{-1} and 1721 cm^{-1} are assigned to C-O stretching vibration, wagging vibration of C-H, C=O stretching and C-H stretching respectively. 780 cm^{-1} shows the aromatic C-H stretching frequency. The relatively broad and intense absorption observed at around 3238 cm^{-1} indicates the presence of bonded O-H stretching vibration from solvent ethanol.

^{1}HNMR Spectral Analysis

The synthesized DHPM derivatives have been characterized by ^{1} HNMR spectral analysis. Figure No.3 shows that the spectral analysis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydro pyrimidine-2(1H)-one B-1 derivative.

^{1}H NMR (DMSO): δ 1.19 (t, 3H, -OCH_2CH_3), 2.37(s, 3H, -CH_3), 4.09 (q, 2H, -OCH_2CH_3), 5.4 (s, 1H, -NH), 5.93 (s, 1H, -CH), 7.28(m, 5H), 8.3 (s, 1H, -NH).

Antibacterial Activities

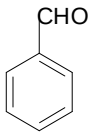
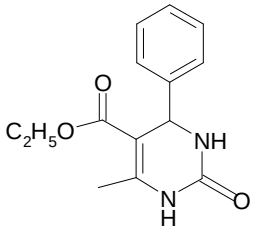
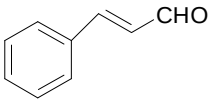
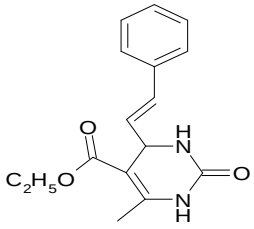
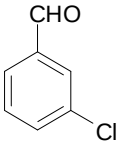
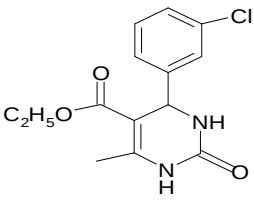
Antibacterial activities of DHPM derivatives were performed using cup plate method by measuring inhibition zone. All the derivatives were screened for antibacterial activities against *Escherichia coli* (gram negative) and *Staphylococcus aureus* (gram

positive) at the concentration of 100 µg/ml. Nutrient agar was used as a culture medium. The plate was inoculated suddenly for preparation of suspension so that the density does not change. The antibacterial activities of the synthesized DHPM derivatives was tested using standard micro dilution method which determines the minimum inhibitory concentration (MIC) leading to the inhibition of bacterial growths of *Escherichia coli* and *Staphylococcus aureus.* The MIC was checked after 24 hrs of incubation at 37^0C. The preparation of micro dilution of DHPM derivatives was done in sterile and aseptic condition to avoid further contamination. Suspended inoculums of *Escherichia coli* and *Staphylococcus aureus* on Petri dish and the medium was inoculated over the entire surfaces of the plate in three directions.

After the inoculums, cups of diameter 5 mm were made in the agar plate with a sterile cork barer. The drug solutions of streptomycin were added to these cups with a micropipette and the plates were then incubated at 37^0C. The inhibition zone was measured using mm scale. The Table No.2 shows that the antibacterial activity data of DHPM derivatives. While the Figure No.4 shows the graphical inhibition zone of *Escherichia coli* and *Staphylococcus aureus*.

From the antibacterial data, it was found that the synthesized compounds shows excellent antibacterial activities against *Escherichia coli* (gram negative) and *Staphylococcus aureus*. (gram positive) at the concentration of 100 µg/ml. The compound B-3 showed maximum inhibition zone 19 mm against *Escherichia coli* while 16 mm against *Staphylococcus aureus.* The standard drug Streptomycin gave 15 mm inhibition zone against *Escherichia coli* and 18 mm against *Staphylococcus aureus.*

Table No.1: Various DHPM derivatives synthesized from different aromatic aldehydes

S.No	Substrate	Reaction Temp.	Reflux Time	Product	Yield %
1		78^0C	20 min.	 **B-1**	98
2		78^0C	30 min.	 **B-2**	93
3		78^0C	45 min.	 **B-3**	95

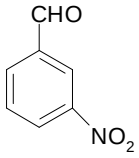
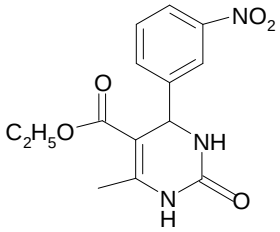
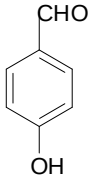
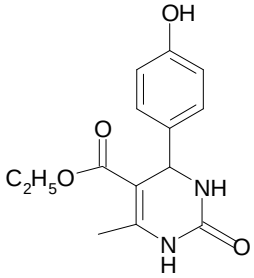
4		78^0C	30 min.	 **B-4**	90
5		78^0C	20 min.	 **B-5**	89

Table No.2: Inhibition zone of DHPM derivatives against *Escherichia coli* and *Staphylococcus aureus*

S.No	DHPM Compounds	Inhibition zone (mm)	
		E. coli	***S. aureus***
1	B-1	13	10
2	B-2	12	14
3	B-3	19	16
4	B-4	10	09
5	B-5	11	12
6	STD	15	18

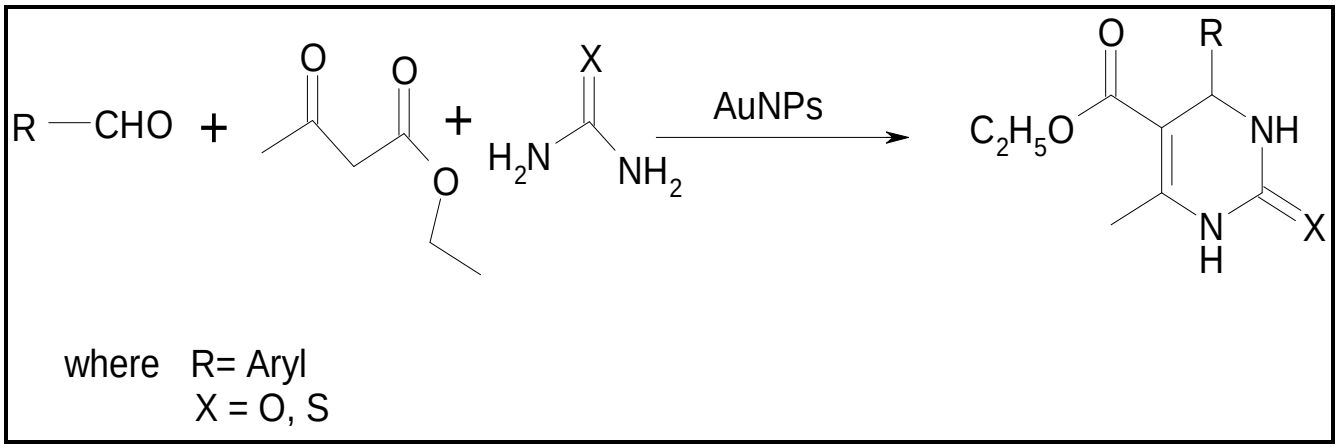


Figure No.1: General Reaction for synthesis of DHPM derivatives

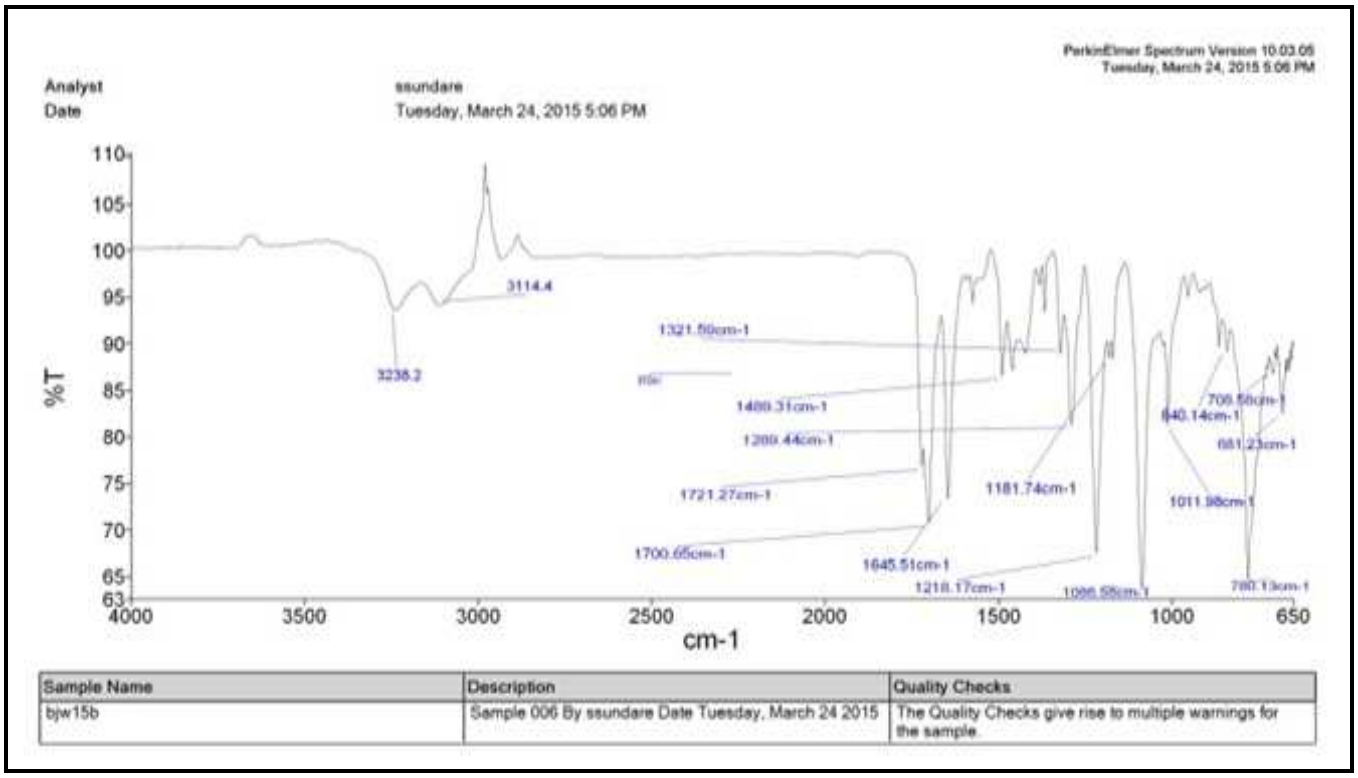
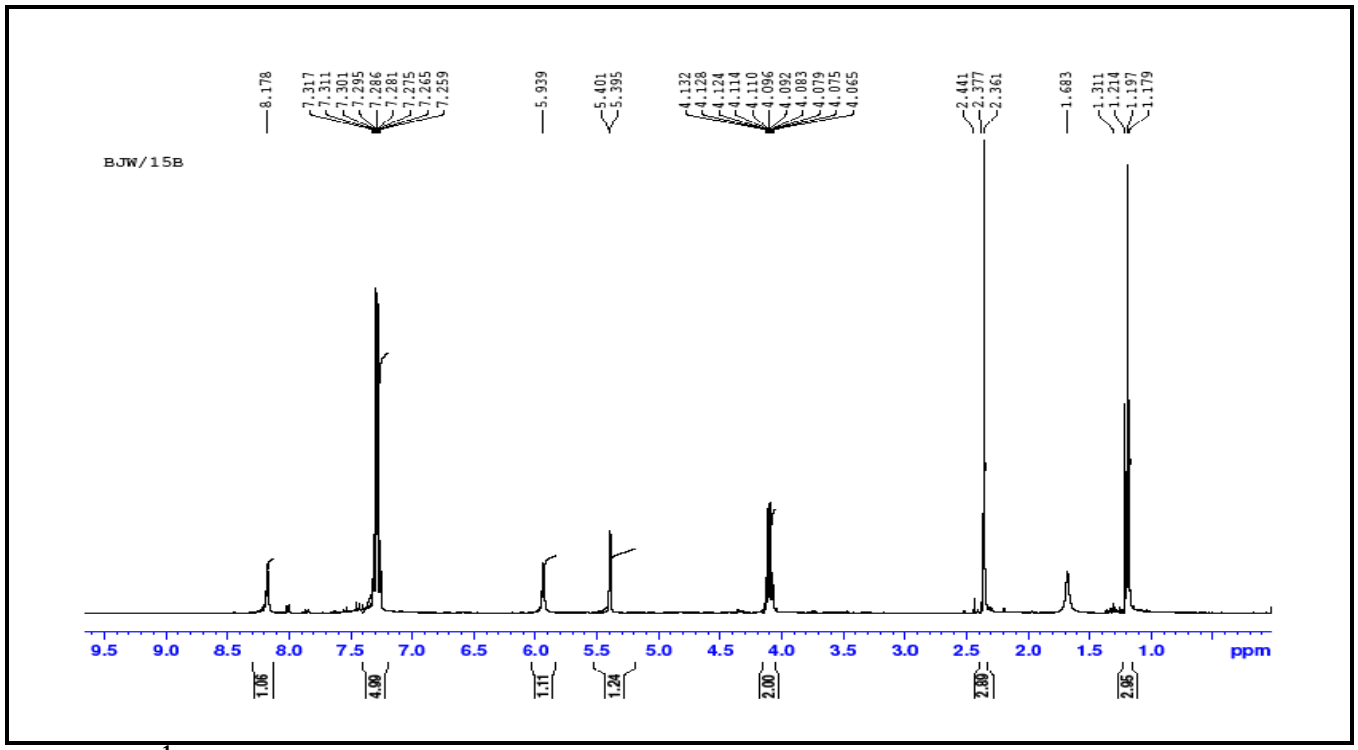


Figure No.2: FT-IR Spectrum of B-1 DHPM derivative



FigureNo.3: [1]HNMR spectral analysis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydro pyrimidine-2(1H)-one (B-1) derivative

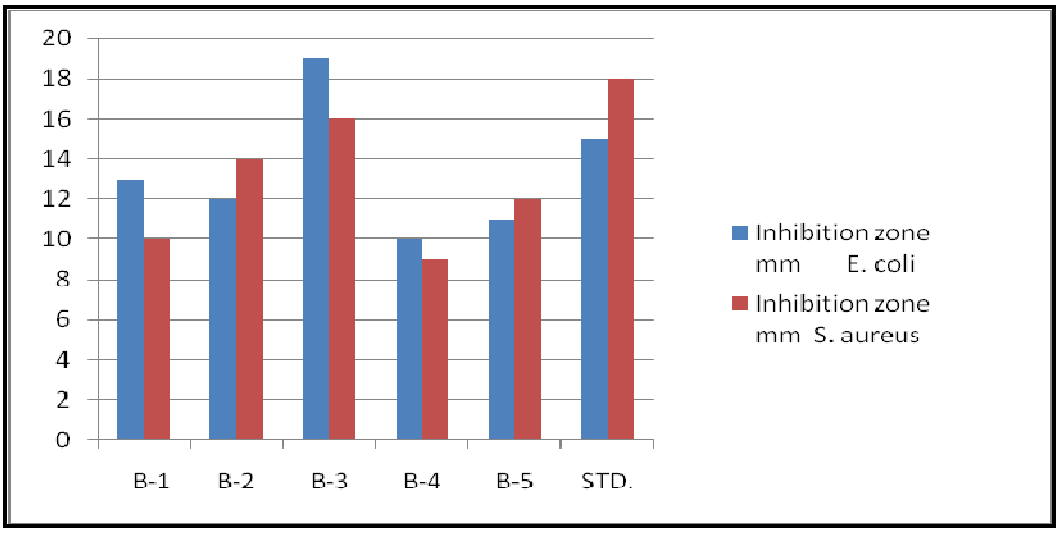


Figure No.4: Antibacterial activity of synthesized activity data of DHPM derivatives

CONCLUSION

We have successfully synthesized various derivatives of 3, 4- dihydropyrimidin-2 (1H) - one (DHPM) by using gold nano particles (AuNPs) as a catalyst. The yield of these derivatives was up to the optimum marks. After the analysis these derivatives are used for antibacterial properties against *Escherichia coli* and *Staphylococcus aureus.* The present study reveals that some of the 3, 4-dihydropyrimidin-2 (1H) - one derivatives (DHPM) could be used as template for the various antibacterial as well as antifungal activities.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Dax S L, McNally J J, Youngman M A. Multi-Component Methodologies in Solid-Phase Organic Synthesis, *Curr. Med. Chem,* 6, 1999, 255-270.
2. Kappe C O. Highly Versatile Solid-Phase Synthesis of Biofunctional 4-Aryl-3,4-dihyropyrimidines using Resin-Bound Isothiourea Building Blocks and Multidirectional Resin Cleavage, *Bioorg. Med. Chem. Lett.*, 10, 2000, 49-51.
3. Heys L, Moore C G, Murphy P J. The Guanidine Metabolites of *Ptilocaulis Spiculifer* and Related Compounds; Isolation and Synthesis, *Chem. Soc. Rev.*, 29, 2000, 57-67.
4. Lu J, Ma H. Iron (III)-Catalyzed Synthesis of Dihydropyrimidinones, Improved Conditions for the Biginelli Reaction, *Synlett,* 10, 2000, 63-64.
5. Gaurav Grover, Suvarna G. Kini. Synthesis and evaluation of new quinazolone derivatives of nalidixic acid as potential antibacterial and antifungal agents, *European Journal of Medicinal Chemistry*, 41, 2006, 256.
6. A Solid-Phase Protocol of the Biginelli Dihydropyrimidine Synthesis Suitable for Combinatorial Chemistry, *Tetrahedron Lett.*, 36, 1995, 7819-7822.
7. Hamaker L K, Yang K, Drane J A, Peterson M L. Proceedings of the Second Lake Tahoe Symposium on Molecular Diversity, *Tahoe City, CA*, January 19-24, 1998.

8. Schreiber S L. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery, *Science*, 287, 2000, 1964-1969.
9. Synthesis and Antiviral Bioactivities of 2- Aryl- or 2-Methyl-3-(substituted-Benzalamino) -4(3H)-quinazolinone Derivatives, *Molecules*, 12, 2007, 2621-2642.
10. Mani Chandrika P, Yakaiah T, Raghu Ram Rao A, Narsaiah B, Chakra Reddy N, Sridhar V, Venkateshwara Rao J. Synthesis of novel 4,6-disubstituted quinazoline derivatives, their antiinflammatory and anti-cancer activity (cytotoxic) against U937 leukemia cell lines, *European Journal of Medicinal Chemistry*, 42, 2007, 147-152.
11. Xingwen Gao, Xuejian Cai, Kai Yan, Baoan Song, Lili Gao and Zhuo Chen. Synthesis and Antiviral Bioactivities of 2- Aryl- or 2-Methyl-3-(substituted-Benzalamino) -4(3H) – quinazolinone Derivatives, *Molecules*, 12, 2007, 2621-2642.
12. Xia Y, Yang Z N, Hour M J, Kuo S C, Xia P, Bastow K F, Nakanishi Y, Nampoothiri P, Hackl T, Hamel E and Lee K H. synthesis, preliminary QSAR study and antimicrobial activity of some novel 2, 3-disubstituted quinazolinone derivatives, *Bioorg. Med. Chem. Lett.*, 11, 2001, 1193.
13. Alagarsamy V, Revathi R, Meena S, Ramaseshu K V, Rajasekaran S and De-Clerco E. Anti-HIV, antibacterial and antifungal activities of some novel 1,4-disubstituted-1,2,4-triazolo[4,3-a] quinazolin-5(4 *h*)-ones, *Indian. J. Pharm. Scien.*, 4, 2004, 459.
14. Pandey V K, Tusi S, Tusi Z, Raghubir R, Dixit M, Joshi M N. Heterocyclic Compounds Thiazolylquinazolones as Potential Antiviral and Antihypertensive Agents, *Indian J. Chem.*, 43, 2004, 180-184.

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