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Review Article

A review on synthetic study and biological activities of tetrahydropyrimidinone derivatives

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ABSTRACT

The process of drug discovery involves the identification, synthesis, characterization, screening, assay and development of new chemical entities that are suitable for medical and pharmaceutical use. 2-thioxo-1, 2, 3, 4-tetrahydropyrimidine (THPM) are heterocyclic compound & represents are markable pharmacological efficient moieties and are with wide range of therapeutic properties. Synthetically they were synthesized using Multi-component reactions like Biginelli reaction or either microwave and conventional methods, having a multiple benefits of the time consuming and get high yield. In this review, we highlight recent developments on THPMs and recently developed as antimicrobial, anticancer, anti-inflammatory, analgesic, antifungal, antibacterial, anti-tubercular, antihypertensive, analgesic, anticonvulsant, antioxidant, etc. given a potent biological and pharmacological activity.

Keywords: Drug discovery; 2-thioxo-1, 2, 3, 4-tetrahydropyrimidine; Biginelli reaction; antioxidant activity; antihypertensive activity

INTRODUCTION

Pharmaceutical chemistry is the core branch of pharmacy education and research. It can be categorized as synthesis of new drug molecule, its analysis and pharmacological studies. The chemistry of heterocyclic compounds is important for the discovery of novel drug. The process of drug discovery involves the identification, synthesis, characterization, screening, assay and development of new chemical entities that are suitable for medical and pharmaceutical use [1]. As a result of remarkable pharmacological efficiency of pyrimidine derivatives, intensive research has been focused on anti-inflammatory activity of pyrimidine nucleus. The present review highlights the synthesis & biological activity of pyrimidine derivatives [2]. During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications, which are anticancer, anti-inflammatory, antibacterial, antiviral, antimalarial,

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anticonvulsant, antihistaminic, antimicrobial [3]. In medicinal chemistry, pyrimidine derivatives have been very well known for their therapeutic applications. Pyrimidine's are of great importance in fundamental metabolism for uracil, thiamine and cytosine are three of the six bases found in the nucleotide. DNA and RNA is one possible reason for the activity [4]. Pyrimidine is an aromatic heterocyclic organic compound similar to pyridine. One of the three diazines, it has the nitrogen atoms at position 1 and 3 in the ring. In recent year, 2-thioxo-1, 2, 3, 4- tetrahydropyrimidine derivatives have received significant attention owing to their diverse range of biological properties particularly being calcium channel blockers. Moreover, 1, 2, 3, 4- tetrahydropyrimidinethione moity is present in many products isolated in natural material such as several specification of sponges. Number of synthetic methods have been developed since BIginelli reaction is very important method for developing 1,2,3,4-tetrahydropyrimidinethione have been synthesized [5]. The THPM have important the integral back bone of several calcium channels modulators and antihypertensive agent, due to which Biginelli multi-component cyclo-condensation reaction received much attention.1,2,3,4tetrahydropyrimidine (DHPM) calcium channels blockers are important class of drugs which induce relaxation of vascular smooth muscle, preferentially in arteries, and display a negative inotropic effect on isolated cardiacmuscle [6].

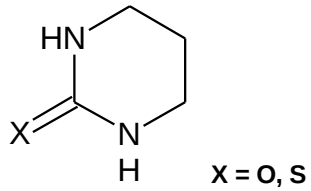
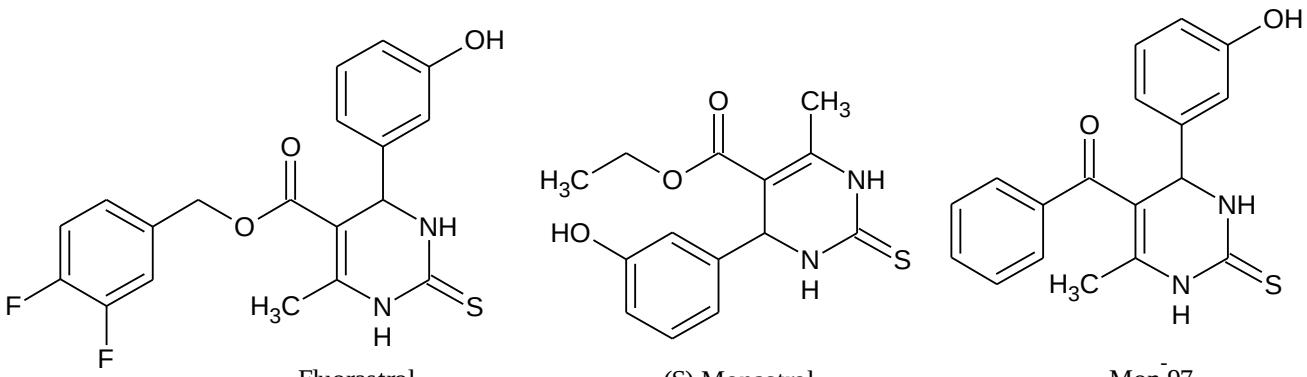


Fig 1: Tetrahydropyrimidinones

The literature indicated that compound having pyrimidine nucleus possesses broad range of biological activity like 5-flourouracil as anticancer; idoxuridine as antiviral; zidovudine as anti-HIV; trimethoprim, sulfadiazine as antibacterial; minoxidil and prazosin as antihypertensive; phenobarbitone as sedative-hypnotic and anticonvulsant; propylthiouracil as antithyroid; thinozylamine as H1-antihistaminics and fervennuline as antibiotics. The literature flooded with report of MCRs of pyrimidine synthesis with numerous variation in catalyst, solvent and starting components [7].

In this review, we present descriptions and discussion on the most relevant synthesis methods and biological activity of 2-thioxo-1,2,3,4-tetrahydropyrimidine derivatives. Some derivatives of 2- thioxo- 1, 2, 3, 4-tetrahydropyrimidine are as follow.



Fluorastrol (S)-Monastrol Mon-97

Fig 2: Natural compound containing THPMs.

Synthetic Strategies: In 2003, the novel three-component condensation reaction of functionalized ethyl acetoacetate, thiourea , aromatic aldehyde reported by A K Padhy and M Bardhan & C S Panda. They found that Hydrazine (NH2NH2) effectively catalyzes the reaction to produce dihydrazide derivatives (5) and again CS2/KOH catalyzes the hydrazide derivatives to produced 4-Aryl-5-(2-aryl-1,3,4-triazolo)-6-Methyl-1, 2, 3, 4-Tetrahydropyrimidine-2-Ones (6) (scheme 01). Derivatives of 4-aryl-5-(2-aryl-1, 3, 4-triazolo)- 6-methyl-1, 2, 3, 4-tetrahydropyrimidine-2-one was obtained by condensed with ethyl bromoacetateto give N3-β-ethoxycarbonyl derivatives and calculated the anti-microbial activity, derivatives of synthesized compound 6b (Ar-C6H5, Ar'-m-NO2C6H5) active against *Staplyllacoccous, E. coli* and *Candida albicans* in Table 1. All these activities were compared with standard drugs chloramphenicol and clotrimazole by measuring the zone of inhibition.

Table 1: Derivatives of synthesized compound

Compound	Ar	Ar'	Yield
6a	C6H5	m-NO2C6H4	60.63%
6b	C6H5	p-ClC4H4	62.38%
6c	C6H5	p-N, N (CH3)2C6H4	67.37%
6d	p-ClC6H4	m-NO2C6H4	55.54%

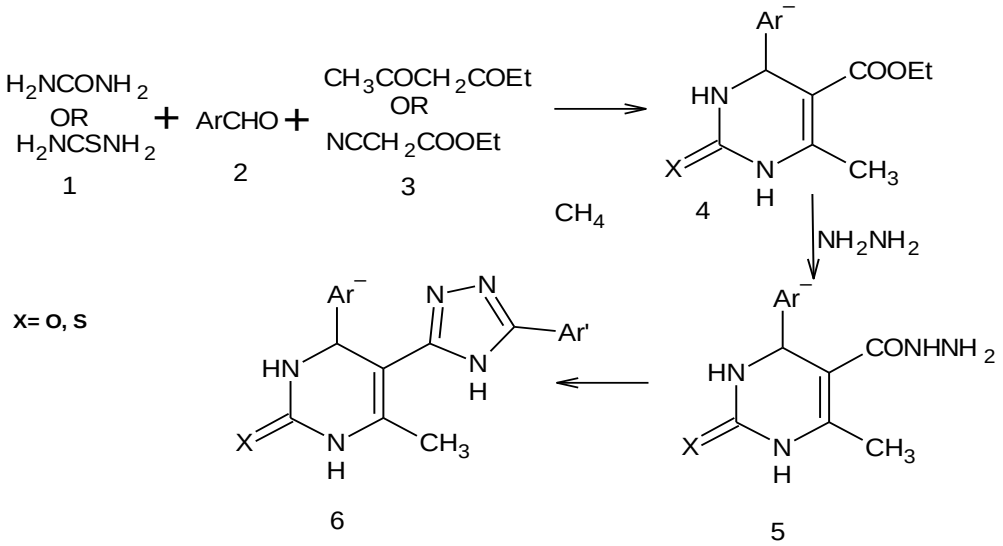


Fig 3: Scheme 01

In 2019, the synthesis of 6(1,3-diphenyl-1*H*-pyrazol-4-yl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitile (2,3) from a three component reaction of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde 1, ethyl cynoacetate2, thiourea3 has been described by Sayed K. Ramadan and Hanan A. S allanin presence of K2CO3/EtOH (scheme 02) Antitumor & Antimicrobial activity evaluation of some of the synthesized product exhibited promising result. Also described the study of anticancer and antifungal activity of synthesized product with variations in result (2, 3). Amoxicillin gives the strong antibacterial activity against *Staphylococcus aureus*and *Escherichia coli.* Fluconazole shows the strong antifungal activity, and doxorubicin shows very strong cytotoxic activity against different human cancer cellline.

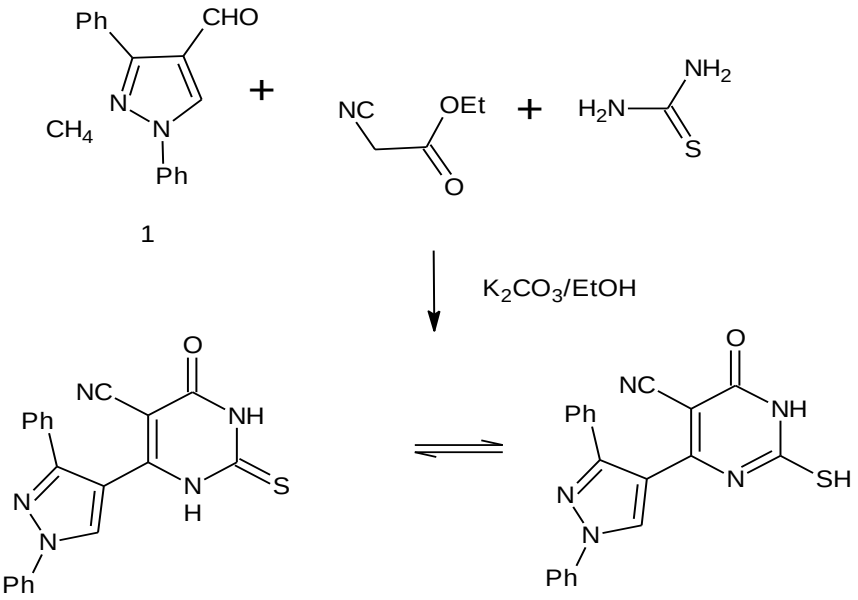


Fig 4: Scheme 02

In 2020, the synthesis and investigation of a new biologically active derivatives of Dihydropyrimidine reported by A. E. Haseynzada, C. Jelsch, H. N. Akhundzada and S. Soudani. Synthesis of 6-methyl-2- oxo-4-(quinolin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4) by Biginelli reaction. The crystal packing is mainly stabilized by strong N-HO hydrogen bonds & aromatic cycle stacking. The crystal structure of synthesized compound was described the view of two independent molecules of the asymmetric unit in the crystal structure and shown 40% probability (scheme 03). The shortest hydrogen bond N5eH5N/O4¼C17 with d (O/H) ¼ 1.96 Å involves an electronegative carbonyl group. Considering that the proposed substance 4 can have an ability to act as an antibacterial drug. The Biological activity of the synthesized compound was studied against the E. coli, P. aeruginosa and S. aureas bacteria. In addition, its activity was also compared with that of pristine antibiotics.

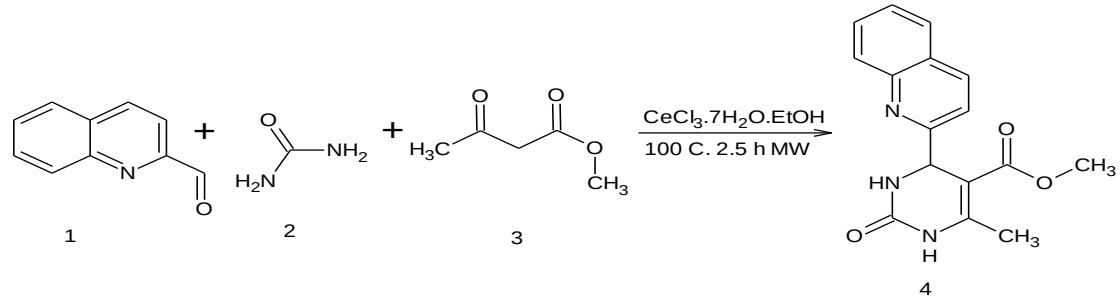


Fig 5: Scheme 03

In 2016, Mounir A. I. Salem & Magda I. Marzouk developed an efficient synthesis of 2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (1) in excellent yield and derivatives (2a-d) were prepared by the reaction of ethyl acetate &thiourea or urea with aldehyde using NH4CL &EtONa as a catalyst (scheme 04). The cytotoxicity and *In vitro* anticancer evaluation of some prepared compounds have been assessed against two different human tumor cell line including breast adeno carcinoma MCF-7 & human hepatocellular carcinoma HepG2. The compounds 2a and 2c shows the moderate activities against Gram-positive and Gram-negative bacteria. Compounds 2a showed moderate degrees of inhibitory activity against hepatocellular carcinoma HepG.

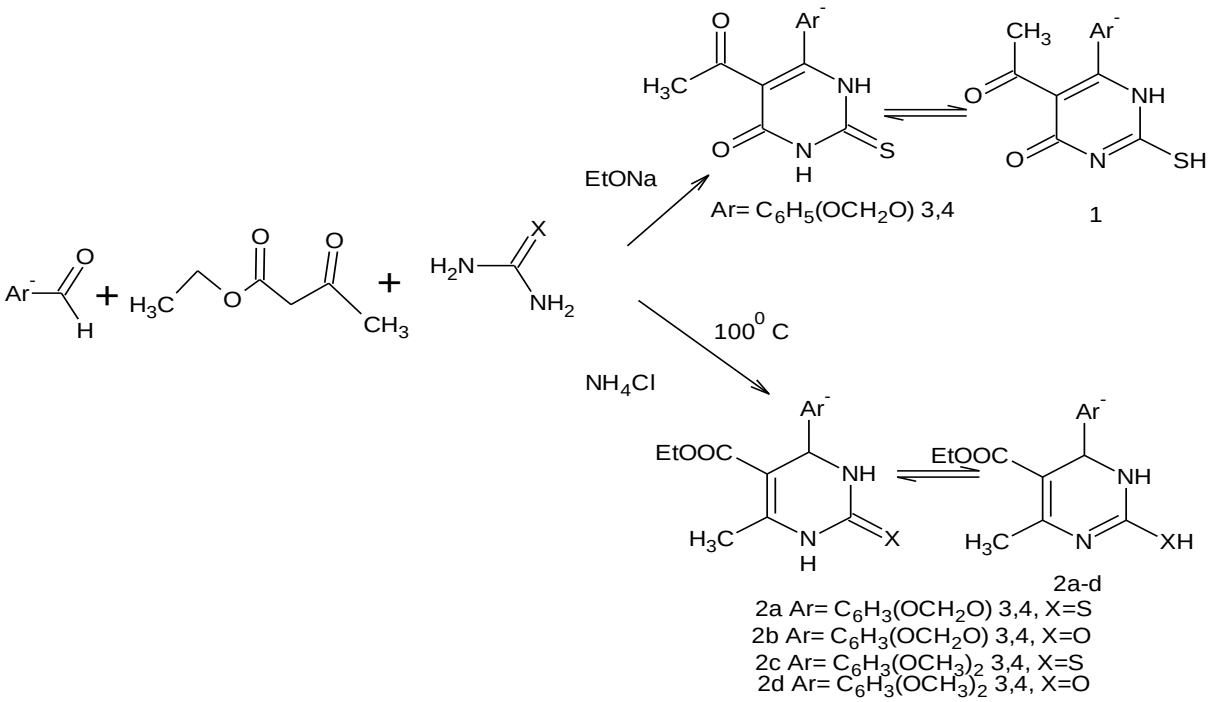


Fig 6: Scheme 04

In 2014, Compound exhibiting high inhibitory activity against superoxide generation by mitochondria in the liver. O. V. Kushnir& co-workers used three component condensation of acetoacetamide, an aldehyde and thiourea in HOAc solution at 50^0C in 65-85% yield, the product 4-aryl-6-methyl-2-thioxo- 1, 2, 3, 4-tetrahydropyrimidine-5-carbamides (scheme 05) were synthesized. Their structure were confirmed by IR & PMR spectroscopy & mass spectroscopy. In antioxidant activity, tests were carried out on 24 female laboratory white rats (110-130g) that were maintained on standard vivarium diet. 2-thioxo-1, 2, 3, 4-tetrahydropyrimidine represent a promising series of compounds for discovering effective tumor-growth agents. Pyrimidinethiones containing 4-phenolic or 3-bromophenyl substituents in the heterocycle 4-position (3) had the most pronounced activity.

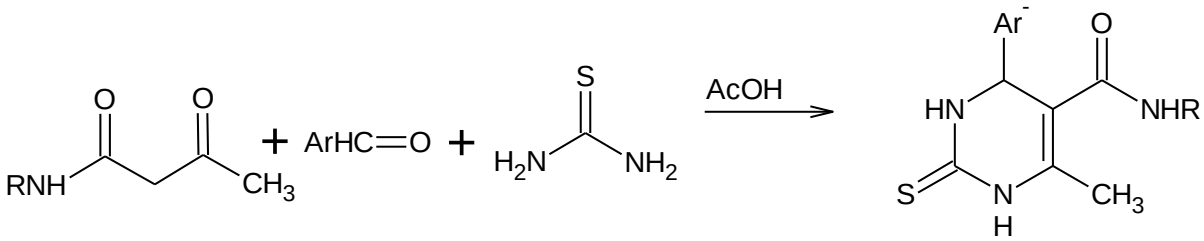


Fig 7: Scheme 05

In 2013, Novel isoniazide cyclocondensation1,2,3,4-tetrahydropyrimidine derivatives by microwave irradiation method was prepared by N-acetoacetyl isonicotinohydrazide with urea/thiourea & appropriate aldehyde in the presence of catalysis amount of laboratory made benzosulphonic acid. The practical percent yield was found 68% and reaction time were found to be 8 minute (scheme 06). Karthikeyan Elumalai, Mohammed Astaf Ali, Manogaran Elumalai and coworkers reported the titled compound exhibited weak, moderate or high antimicrobial & antimycobacterial activity. The in vitro antibacterial activities were tested against Gram-positive bacteria Bacillus subtitles (B. subtalis) and Gram-negative bacteria Escherichia coli (E. coli) by standard serial dilution method using a stock solution of 100g/mL concentration. Fluoride and chloride substitution at fourth position of phenyl ring showed potent antimicrobial and antimycobacterial action because of strong electron Withdrawing nature. Substitution of chloro group at third position of phenyl rings how potentaction when compare with nitroatom.

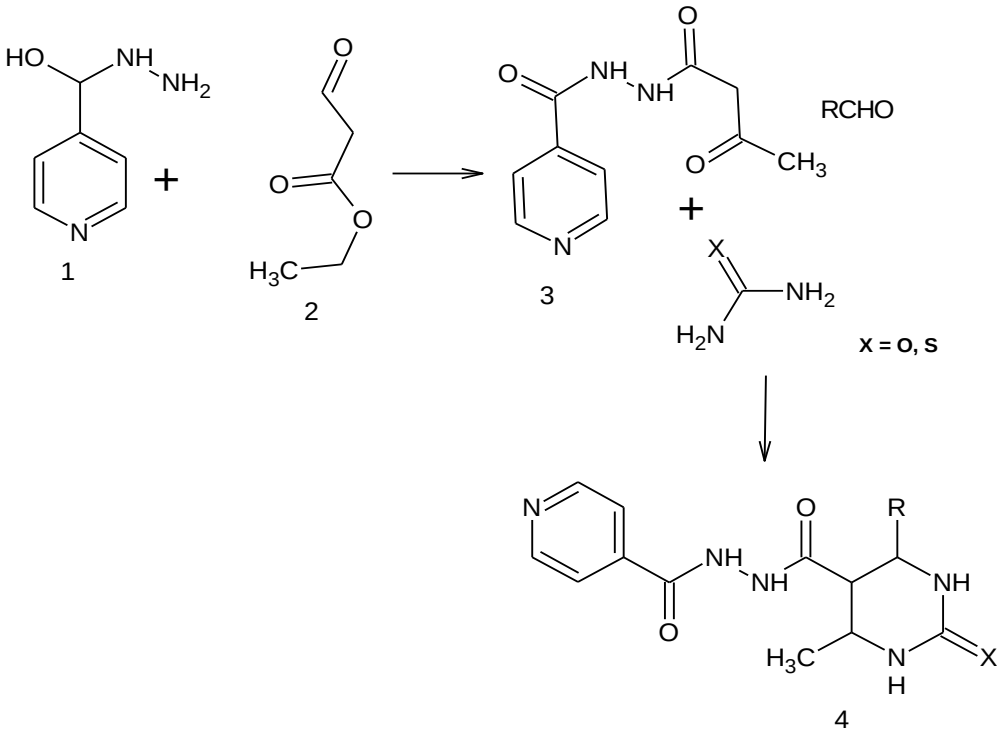


Fig 8: Scheme 06

In 2008, A number of pyrimidine derivatives (scheme 07) have been reported by Ramesh L. Sawant& Manish S. Bhatia, 5-Acyl-6-methyl-4-substituted-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidines were synthesized by cyclocondensation reaction between appropriate aldehyde, acetoacetate and urea/thiourea i n presence of aluminium chloride and hydrochloric acid. (Scheme 07) The synthesized Compounds have been tested for antibacterial activity against *Staphylococcus aureus* & screening and QSAR studies to investigate the relationship between the various physicochemical parameters and antibacterial activity of synthesized 3-benzoyl derivatives of 5-acyl-6-methyl-4-substituted-2 Oxo/thioxo-1, 2, 3, 4-tetrahydropyrimidines (Table 2).

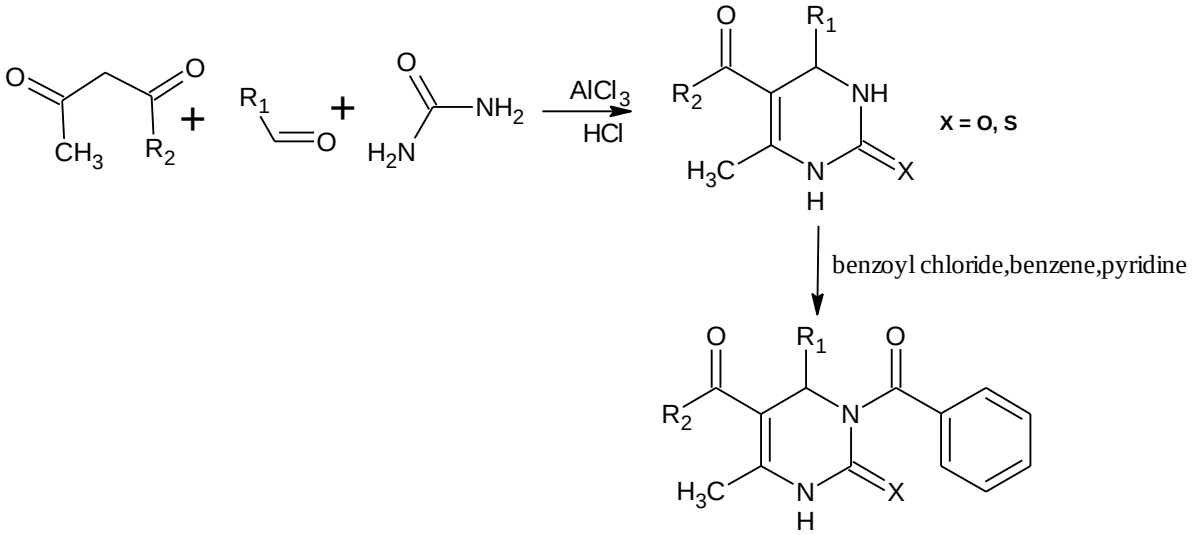
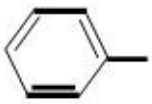
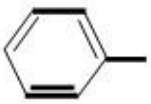


Fig 9: Scheme 07

Table 2- Derivatives of synthesized compound in scheme 07

Scheme		R1	R2	X	Yield
A		CH_3	OC_2H_5	O	66.63%
B 40.00%		CH_3	OC_2H_5	O	
C 67.60%		CH_3	OCH_3	O	

BIOLOGICAL ACTIVITY

The pyrimidine derivatives in general are biologically active and have remarkable antimicrobial, anticancer, anti-inflammatory, analgesic, antifungal, anticonvulsant, etc. [Fig. 10]. As a result of remarkable pharmacological efficiency of pyrimidine derivatives, intensive research has been focused on anti-inflammatory activity of pyrimidine nucleus. Inpresentre view, biological activity reported the synthesized scheme active against various groups. This article aims to review the recent works on pyrimidine derivatives together with the biological potential during the past years.

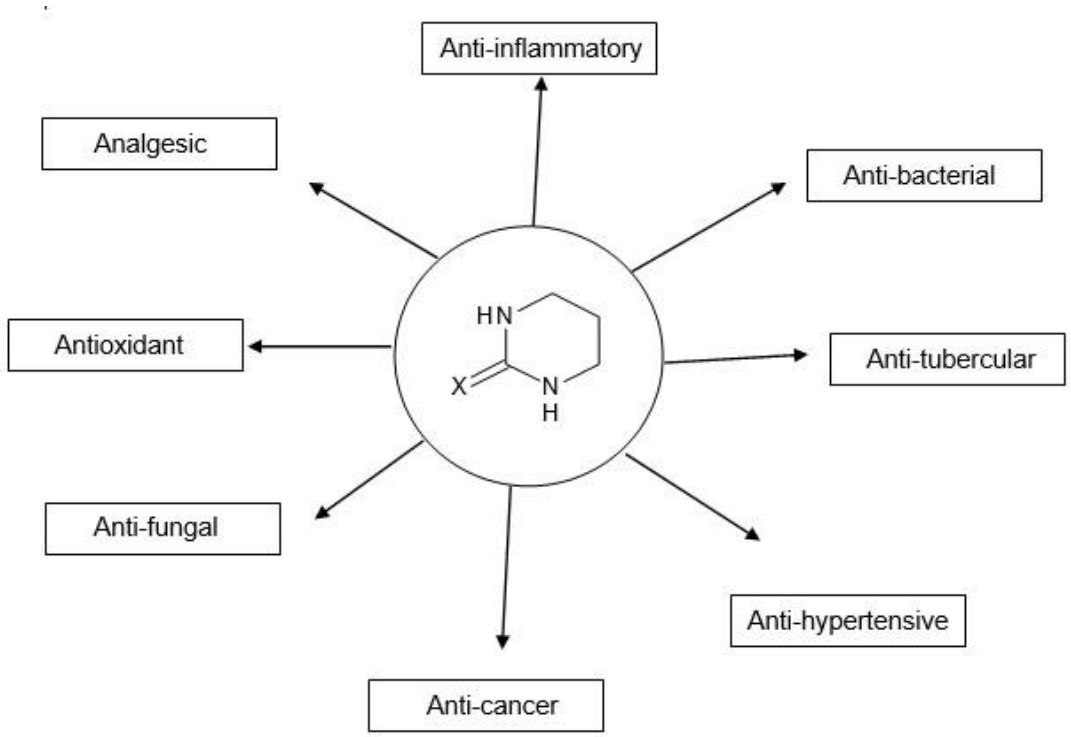


Figure 10: Biological activities of Tetrahydropyrimidines.

Anti-inflammatory Activity: In 2013, Vinayak K. Deshmukh synthesize and evaluated some substitutes 1, 2, 3, 4- tetrahydropyrimidine derivatives as potential anti-inflammatory agents. All compounds were screened for in-*vitro* anti-inflammatory activity by inhibition of protein denaturation method using diclofenac as a standard drug. The results revealed that almost all the tested compounds showed potent in in-vitro anti-inflammatory activity. Derivatives 1,2,3,4,5, showed significant in-*vitro* anti-inflammatory with % inhibition of albumin denaturation 98%, 97%, 90%, 94%, 94%, and 96% respectively (Fig. 11). At the same all these compounds have very good drug score 0.74, 0.53, 0.39, 0.38, 0.4, as none of the compounds has any toxicity [17]. The presence of 4-methoxy group at C-4 plays an important role in the activity of compound.On the other hand, C-4phenyl group reduced the activity of the compound at C-4 & 4-methoxy phenyl at C-6 then the activity of the compound was found to be increased. [18].

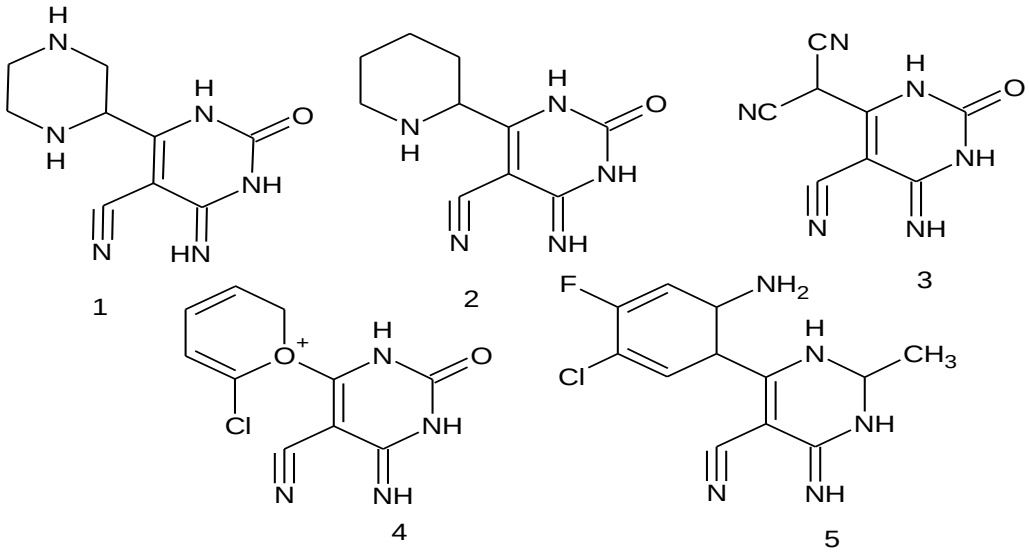


Figure 11: The structure of potent anti-inflammatory compound

Antimicrobial Activity: In 2014, KarthikeyanElumalai et al. synthesized compound were subjected to in-vitro antimicrobial activity against Gram-positive bacteria *B. subtilis*, Gram-negative bacteria *E. coli* by standard serial diluation method using stock soluation of 100µg/ml concentration. Nutrient broth was used as culture media and dimethyl sulphoxide (DSMO) was used as solvent control. Norfloxacin (Nfn) was used as standard drug. The inoculated test tubes were inoculated at 37 ± 1˚C for 24 h. All the 1,2,3,4-tetrahydropyrimidines were potent antimicrobial agent, with an MIC value ranging from micromolar to submicromolar. In 2017, Naser Foroughi far et al. reported the antibacterial activity of some synthesized compounds, three-gram negative bacteria: *Esherichia coli* (ATCC 25922), *Klebsiellapneumoniae* (ATCC 13883) and *Pseudomonas aeruginosa* (PAO1) and three-gram positive bacteria: *Staphylococcus aureus* (ATCC 6538), *Staphylococcus epidermidis* (ATCC 12228), *Bacillus cereus* (ATCC 14579) were selected and tested by the disc diffusion method using Mueller–Hinton agar against. Cephalexin was used as the standard. Normal saline was used for preparation of inoculants having turbidity equal to 0.5 McFarland standards. Dimethyl sulfoxide (DMSO) was used as solvent control for the preparation of stock solution. Culture was carried out with sterile swab and microtube suspension was cultured for 24 h and then inoculated onto Mueller Hinton agar. Blank discs with a diameter of 6 mm and containing 30µg of the concentration of the compounds (1-10) were placed on Muller Hinton agar medium. After 24hr incubation at 37°C, zones of growth inhibition were measured. The Compound 1- 4, 6, 8-10 shows antibacterial activity against gram negative bacteria (Fig. 12). Compounds 2 and 8 showed considerable inhibitory activity against P. aeruginosa but the other compounds did not show any activity against P. aeruginosa [19]. It is concluded that compounds which had OCH3 and Cl substitution at any position of the C-4 phenyl group showed antimiceobial activities at lower concentration. A substituted benzoyl methyl thio group located on the C-2 position of the THPM ring seemed to be effective in the antimicrobial activity. Tetrahydropyrimidines possessing bulkier group at C-4 position were also subjected to antimicrobial assessments [20].

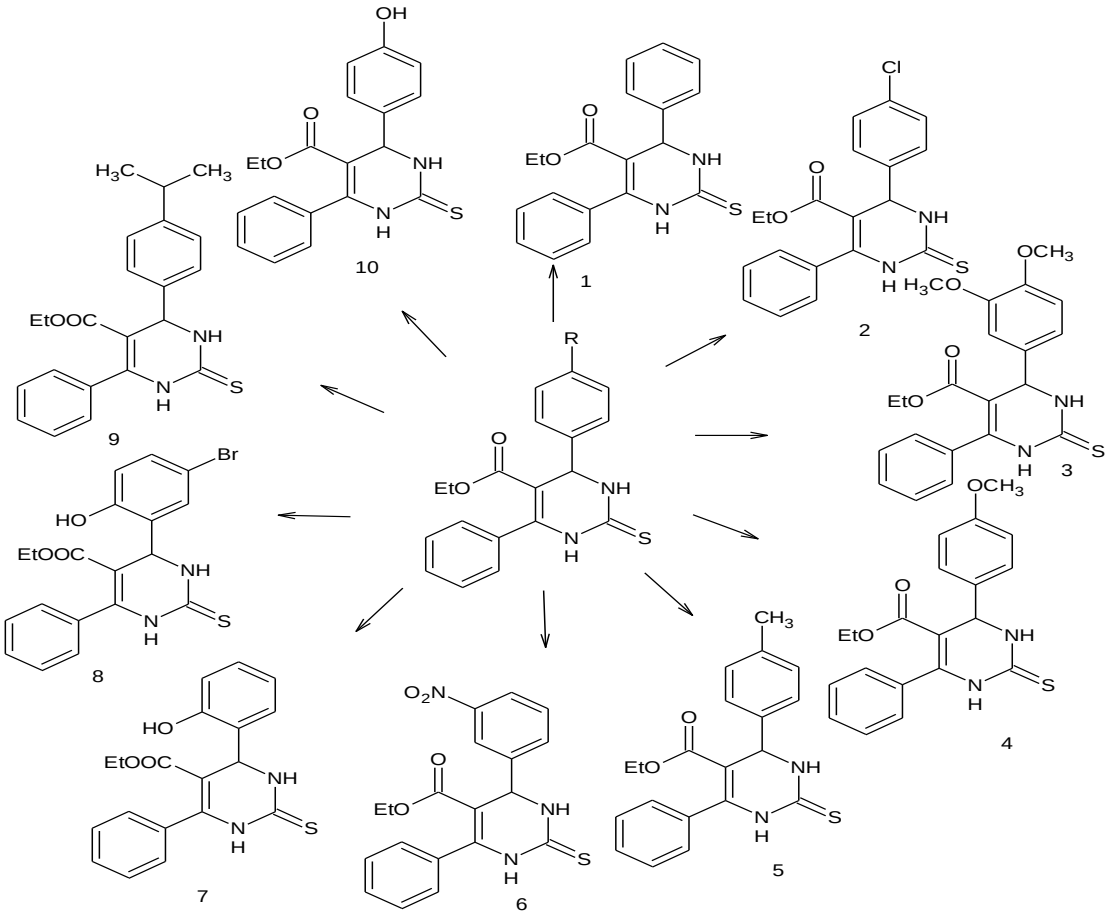


Figure 12: The structure of potent THPMs having Anti-bacterial activity.

Antioxidant Activity: In 2014, Kushnir et al. synthesized 2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbamides (A) derivatives evaluated for antioxidant activity. The rate of mitochondrial superoxide generation gives the ffect of a (6-10) were studied *invitro* experiments. The DMSO concentration in the solution for determining superoxide was ≤1% of the total sample volume. A mitochondria fraction (0.05mL) sample was treated with the Biginelli compounds to a final concentration of 10^{-3}M and incubated at 37^0C for 5 min in solution for detecting superoxide anion-radical generation. Compound exhibiting high inhibitory activity against superoxide generation by mitochondrial in the liver and in transformed tissue of tumor-bearing rats were discovered. Pyrimidinethiones containing 4-phenolic or 3- bromophenyl substituents in the heterocycle 4-position (A6-9 and 10) had the most pronounced activity (Fig. 13). These inhibited by 3 – 7 times the production of superoxide anion-radical in mitochondria of tumor-bearer liver and by 2–3 times, in Heren's carcinoma tissue [21].

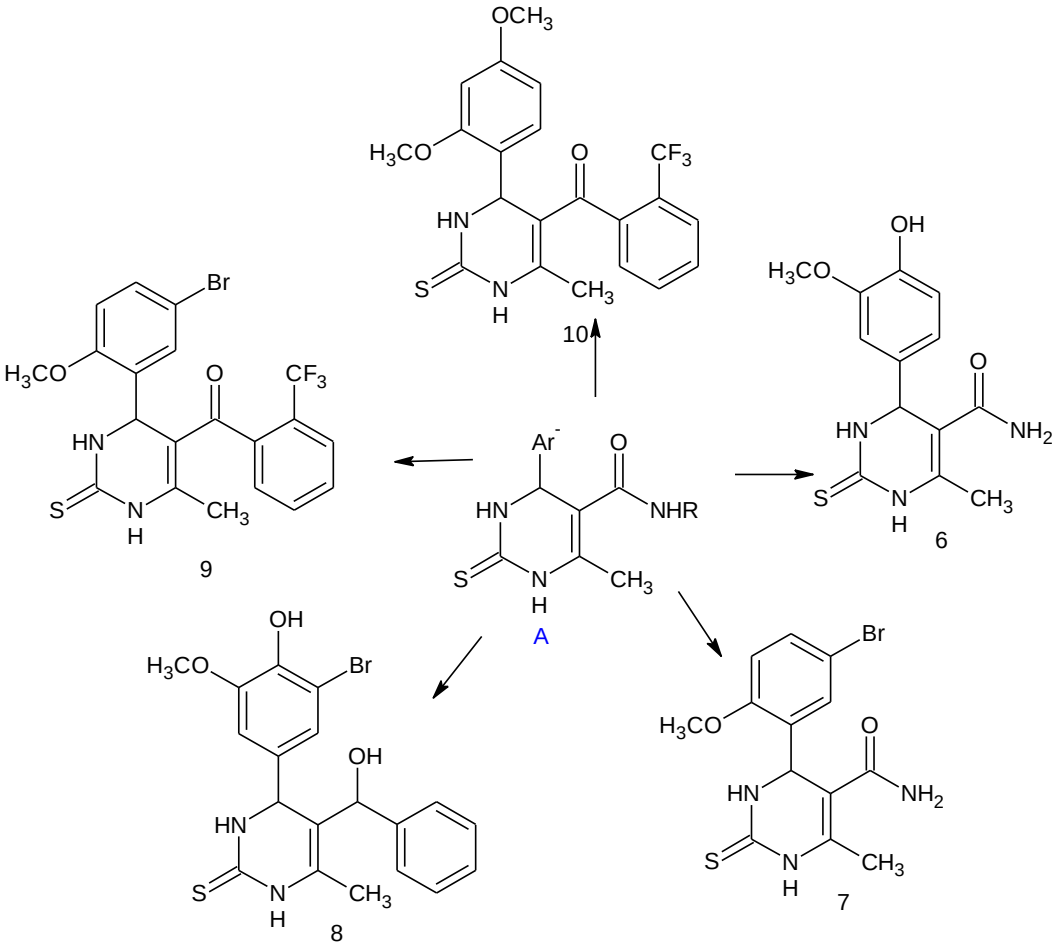


Fig 13: The structure of potent Antioxidant compound.

Analgesic Activity: In 2011, NOFAL et al. synthesized some mono, bi- and tricyclic pyrimidine derivatives and evaluated for the central analgesic activity. Central analgesic effect of the synthesized compounds was examined using hot-plate technique. All compound showed significant analgesic effect after 60 min of drug administration (50mg/kg) compared to base line reading. Mice were introduced to electronically controlled hot-plate surface adjusted to 52±0.1˚C (7280 Hot-plate module, Ugo Basile, Comerio, Italy) at 0, 1, 2 h after oral administration of tested compound (50mg/kg). Time required for mice to lick paw/jump was recorded using built-in digital timer and designated as withdrawal latency (WDL). Compound 11, 12, 13 and 14 showed longer withdrawal latency compared to tramadol (20mg/kg) 60 min after drug administration. (Fig. 14) However, all tested compounds, except 15, remain their analgesic potency up to 120 min after drug administration. All the tested compounds showed significant analgesic effect due to the presence of heterocyclic penta atomic nucleus (pyrazole, pyrazolone, pyrazolidindione) at position 5 of the pyrimidine moiety [22].

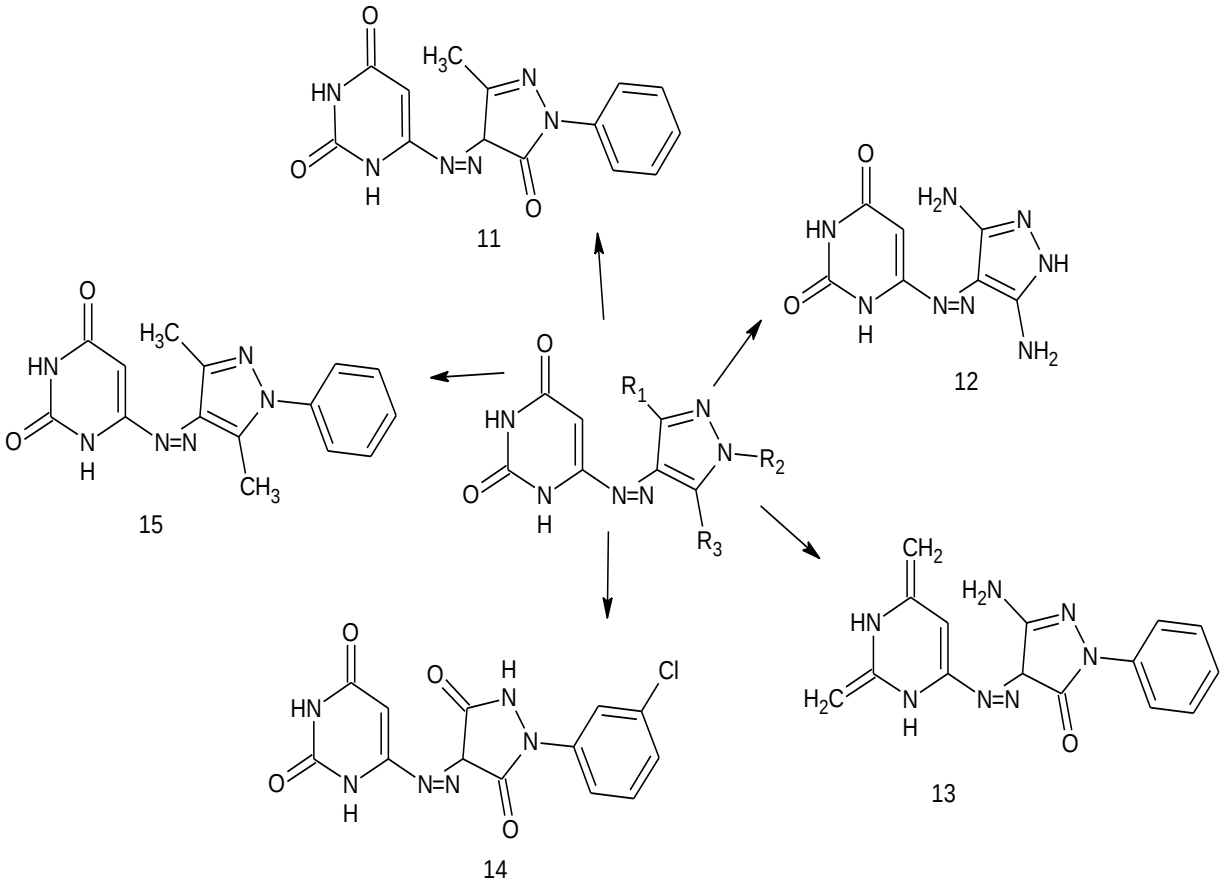


Figure Fig 14: The structure of potent analgesic compound.

Antihypertensive activity: In 2009, Chikhale et al. synthesized new ethyl 6-methyl-2-methoxy-3-(substituted-1-phenylethanone)- 4-(substitutedphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylated as antihypertensive agents. The ten compound were tested for antihypertensive activity by non-invasive tail-cuff, and evaluated by carotid artery cannulation method for determining the diastolic blood pressure. Hypertension was induce by DOCA-salt. Test compounds 16, 17, 18, 19, 20, 21, 22, 23 exerted comparative antihypertensive activity at 10 mg/kg dose level compared to nifedipin (Fig. 15). Structure-activity studies we choose the aromatic substitutions that are commonly employed in dihydropyrimidin. 4-methoxy derivatives 22 has remarkable antihypertensive activity. 3, 4-disubstituted methoxy derivatives 23 has shown good antihypertensive activity at 10 mg/kg. Those compound that showed significant activity by tail-cuff method were further evaluated for their antihypertensive activity by direct cannulation of the caroid artery [23].

Antifungal activity: In 2015, Zamaraeva et al. studied antibacterial as well as antifungal activity of seven tested compounds were in vitro evaluated using agar well diffusion test. The compounds (100 µg/ml) dissolved in 1ml DMSO as a qualitative method for studying the antifungal activity of the tested compounds against the following tested stains; fungal strains are Candida albicans and Aspergillus flavus.

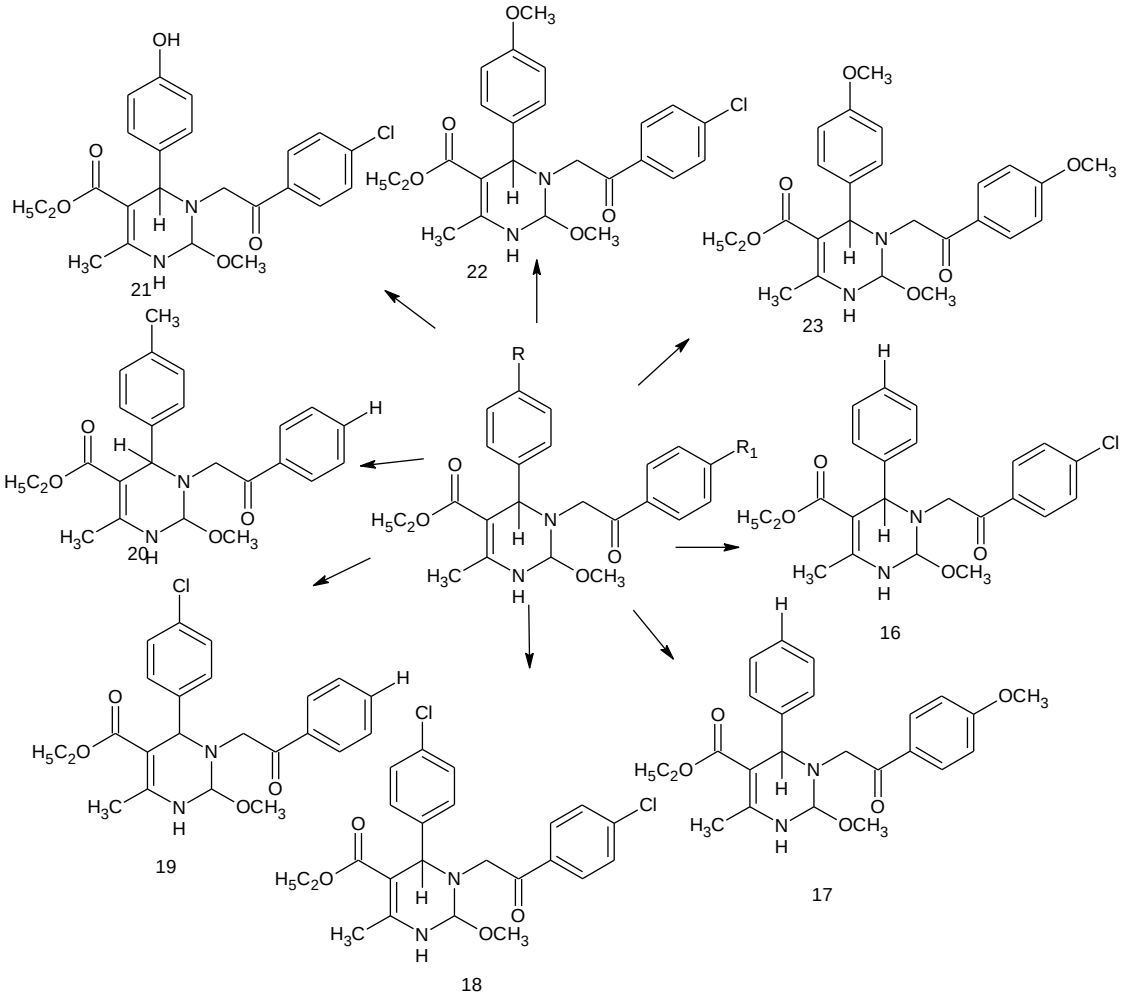


Figure 15: The structure of potent Antihypertensive compounds

The antifungal activity measured by agar well diffusion method. On the other hand, it was found to be inactive against the Candida albicans fungus.

The antifungal activity was studied for five compound 24,25,26,27,28 [Fig. 16] [24].

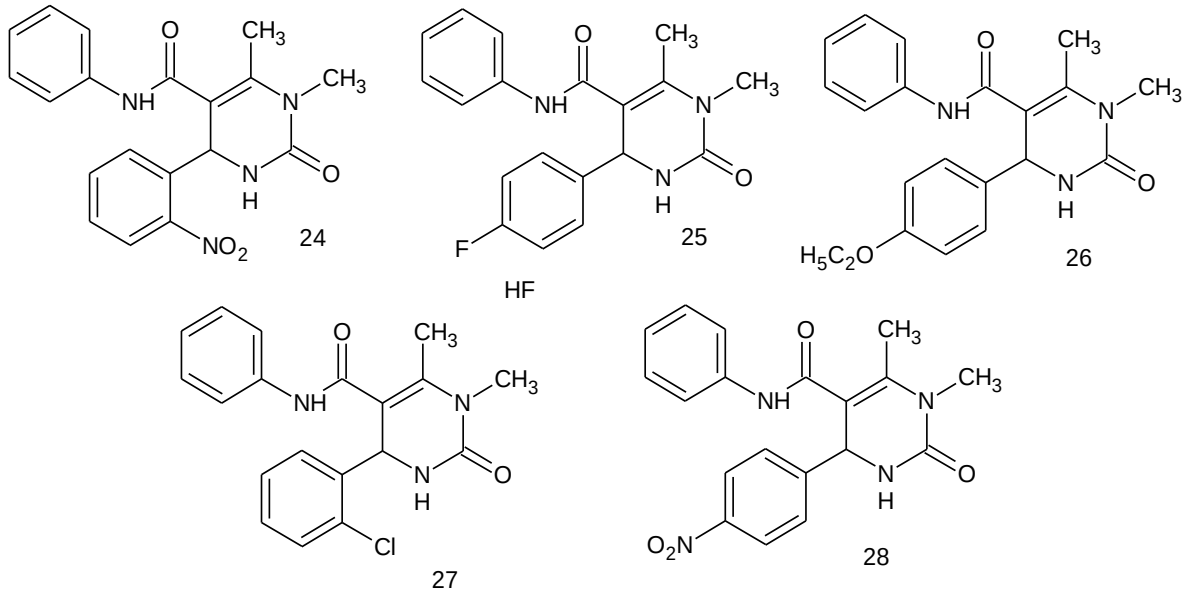


Fig 16: The structure of compound possessing Antifungal activity.

Anticancer Activity: In 2016, Mounir Salem et al. evaluated the anticancer activity of synthesized compound Tetrahydropyrimidinethione. The anticancer activity evaluated by *in vitro* via the standard MTT method against a panel of two human tumor cell lines namely: hepatocellular carcinoma HepG2 and against HepG2. The highest toxicity shows the 30 and 35, which gives the % viability IC50 at 38.5 and 43.2. Also compounds 29, 31, 32 and 33 showed weaker against HepG2 (Fig. 17) Compound 28 and 30 showed moderate anticancer activity against breast cancer MCF-7 with % inhibition 42.5 and 42.7 μ mol/L.The presence of the electron withdrawing group on the phenylamino moiety was the enhancing factor in the anticancer activity of the synthesized compound against HCT-116. Also, the existence of an Oxo moiety at the C-2 position of the tetrahydropyrimidine ring improved the anticancer activity against both tested celllines, although at hioxomoirty did not significantly improve the anticancer activity [25].

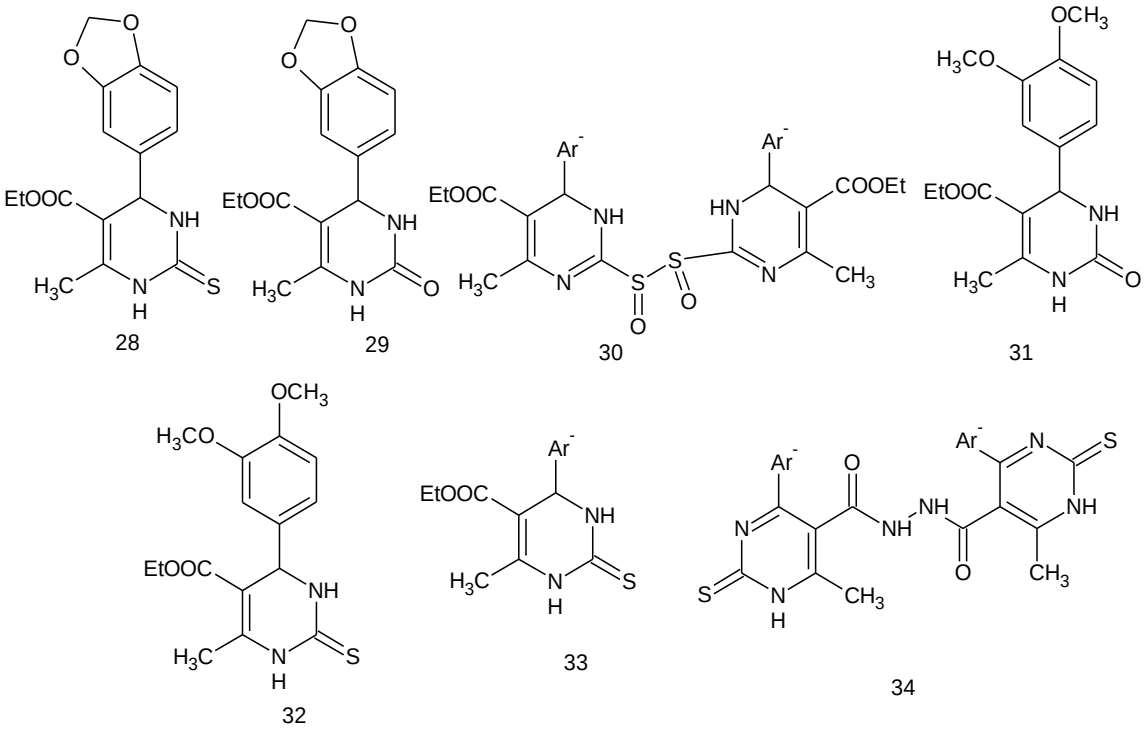


Figure 17: The structure of potent anticancer compound.

Anti-tubercular Activity: In 2008, Vijay Virsodia et al. synthesized substituted *N*-phenyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4- tetrahydropyrimidine-5-carboxamides as anti-tubercular activity. All compound were screened for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain by resazur in microplate assay plate method. Methyl group at these positions showed higher potency. But substitute on son 4-phenyl ring also alter the activity of compound. Compound 35 is having 3,4-dimethylphenyl carbamoyl side chain as in compound 36, but NO2 group is at m-position in compound 37 and p-position in compound 35 which leads to decrease in % inhibition from 63% to 13% (Fig. 18). Thus, the methyl groups phenyl ring at C-5 side chain with meta substitution 4-phenyl ring showed good potency [27].

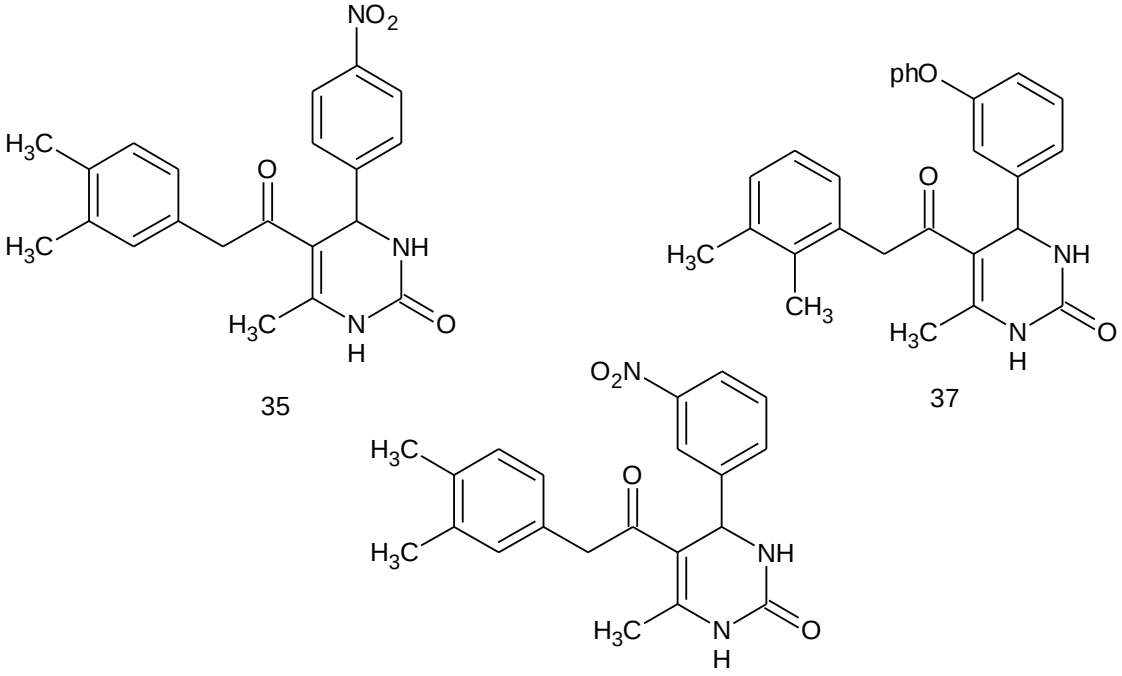


Figure 18: The structure of potent antitubercular compound.

CONCLUSION

This review summarizes the synthesis of Tetrahydropyrimidinones derivatives and its biological activities. The synthesis of pyrimidine derivatives done by three-component condensation with different catalytic activity and gives different biological activity. In which tetrahydropyrimidine derivatives is act as a induce relaxation of vascular smooth muscle, preferentially in arteries, and display a negative inotropic effect on isolated cardiac muscle. Various substituted phenyl, chlorophenyl, quinolone or aryl as well as number of heterocyclic moiety have been incorporated at 4-position. Most of the tetahydropyrimidine have methyl group at 6-position and also modified the 5-position with different group. Compounds are reported biological activities such as antibacterial, antifungal, antimicrobial, anti-inflammatory, analgesic, anticancer, cytotoxic, antioxidant, antitubercular, antioxidant, etc.

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