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Design, Synthesis and Study of Fused 1,4 dihydroPyrimidines of Biological Interest-A Review

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ABSTRACT

The challenge in chemistry is to develop practical processes, reaction media, conditions and utility of materials, based on the idea of green chemistry. Thus in order to meet the scientific challenges, of protecting the human health and environment and also simultaneously achieving commercial viability, some bio-active compounds are synthesized through MORE (Microwave-assisted organic reaction enhancement) technique as it is easy, effective, economical and eco-friendly. The present review includes pyrimidines, quinazolines and their fused derivatives, which have great significance in life as these structural subunits exist in many natural products. As dihydropyrimidines are potent mimics of dihydropyridines, so they can act as calcium channel blockers as the latter. Besides this, the compounds containing pyrimidine nucleus, have shown antimicrobial activities too. Some other derivatives like, pyrimidine and quinazoline thiols come out to be anti-convulsive in nature. In spite of the pharmacological action, the latter derivatives acted as vulcanization accelerators also. Thus, the present review is a kaleidoscope of various properties of different, bioactive compounds.

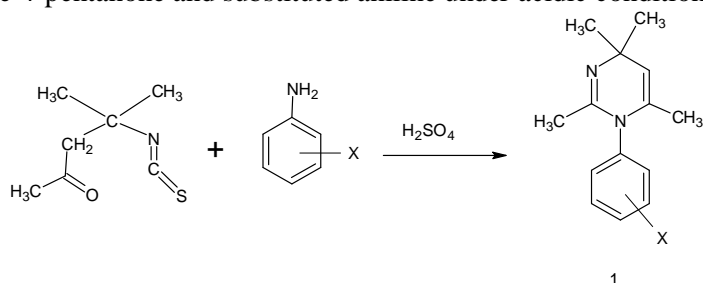
Keywords: Green chemistry, MORE technique, Calcium channel blockers, Antimicrobial activities, Anticonvulsant.

INTRODUCTION

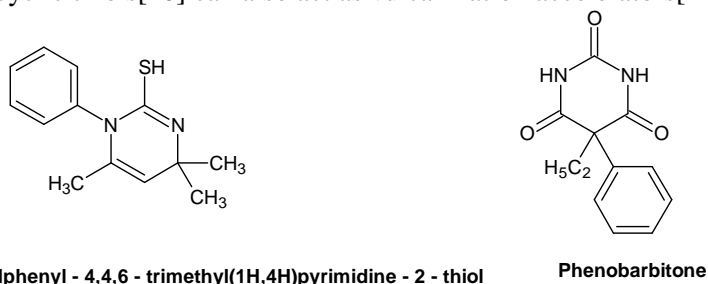
A wide variety of heterocycles have been explored for developing pharmaceutically important molecules. Among all these, the compounds of our interest are, fused pyrimidines and their derivatives. This is because pyrimidines[1-6] acquired a special place in heterocyclic field due to their diversified activities such as anti-viral, anti-tumor, anti-bacterial, and anti-inflammatory. Besides this, benzo fused pyrimidines like quinazolines (i.e. benzodiazines in which nitrogen atoms are in position 1,3-) are also included in our discussion. This is because, quinazoline chemistry has received some attention in recent years. Their large no. of biological actions[7-18] like antifungal, anti-tumor, anti-cancer, anti-HIV, anti-inflammatory, anti-bacterial, anti-malarial etc. has prompted us to compile work on this category of compounds also. Keeping this in view, a lot of work was done in our lab, comprising the above discussed derivatives, and this review throws light on it.

ANTI-CONVULSANT ACTIVITY

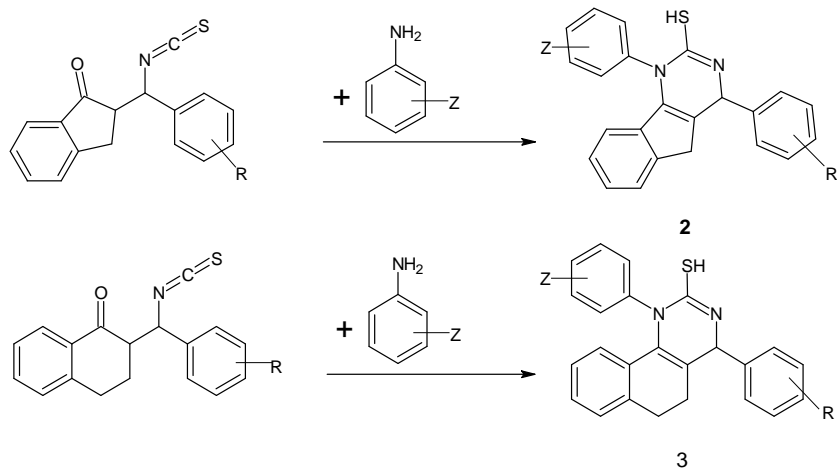
1-substituted phenyl-4,4,6-trimethyl-1,4-dihydropyrimidine-2-thiols (1) were prepared using 2-methyl-2-isothiocyanate-4-pentanone and substituted aniline under acidic conditions.



These compounds have been prepared, as of phenobarbitone as a model which is an anti-convulsant drug[19]. The comparison between the two structures i.e. phenobarbitone and pyrimidine system, is obvious. Besides this, heterocyclic thiols[20] can also act as vulcanization accelerators[21].



Keeping in view, the significant biological properties associated with the above moieties, synthesis of 1,4-diaryl-4,5-dihydro-1*H*-indeno[1,2-*d*]pyrimidine-2-thiols(2) and 1,4-diaryl-1,4,5,6-tetrahydrobenzo[*h*]quinazoline-2-thiols (3) were carried out[22].



Two different techniques were used for finding anti-convulsant activity:

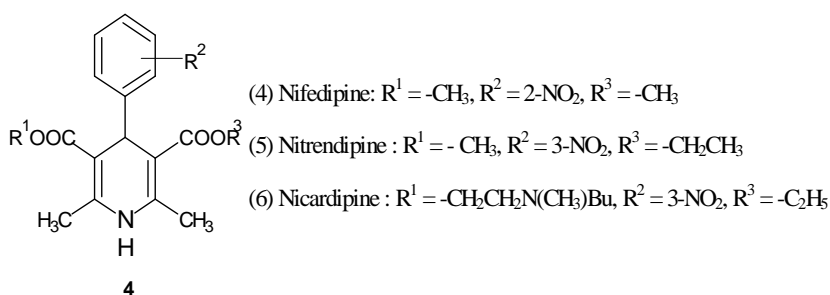
1. Maximal Electroshock Seizure Control Test
2. Chemoshock or Leptazole Seizure Threshold Test

Electroconvulsimeter apparatus was used for this purpose. The first technique used was as described by Toman et al[23] and the second technique was set up as described by Swinyard et al[24]. In both these techniques, thirty Albino mice of either sex, each weighing between 20-60 gms were taken. These were divided into three groups. In Group-I (Control Group) animals, distilled water was injected and in animals of Group-II & III phenobarbitone and test compound respectively was injected. The dose of each animal was calculated according to the body weight of mice. These injections were given intraperitoneally in the

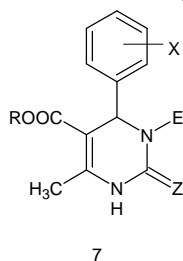
left lower quadrant of the abdomen of mice. In all the three groups observations were recorded separately and inter group comparison were made. It has been found that as the concentration of test compound 1-(4-nitrophenyl)-4,4,6-trimethyl-1,4-dihydropyrimidin-2-thiol is increased from 10 mg kg⁻¹ to 80 mg kg⁻¹ weight, anticonvulsant activity increases in the experimental animals. When compared to Phenobarbitone, a standard drug used in the treatment of Epilepsy, it has been found that test compound has shown comparable anticonvulsant activity. Further it has been found that nitro-substituted phenyl compounds have shown greater anticonvulsant activity as compared to other substituents (X= Cl, H, CH₃, OCH₃) in preliminary studies as nitro substituted compounds are more soluble than other derivatives.

CALCIUM CHANNEL BLOCKING ACTIVITY

Literature survey reveals that among a large variety of pyrimidine derivatives, dihydropyrimidines are associated with broad spectrum of biological activities ever since 4-aryl-1,4-dihydropyrimidines (DHPs) of Nifedipine type 4 were first introduced into clinical medicine in 1975. Even today, DHPs are the most potent calcium channel modulators available for the treatment of cardiovascular diseases[24].



Actually, dihydropyrimidines are described as potent mimics of dihydropyridine calcium channel blockers[25-30] e.g. (5) and (6). Recently much interest has been focused on the chemistry of 2-thioxotetrahydropyrimidin-5-carboxylic acid and their derivatives known as Biginelli's compounds[59]. When properly substituted they can act as cardiovascular agents[30,60] which is not surprising since they can be regarded as aza-analogs of Nifedipine related dihydropyrimidines of type 7. Studies show that vinylogous urethane portion[30] of dihydropyrimidines is required for biological activity.



R = alkyl; Z = O, S; X = e.g. 2/3-NO₂, 2-CF₃; E = ester, acyl, amide

The solid state structure of dihydropyrimidine analogs show that these compounds can adopt a molecular conformation which is similar to the reported conformation of dihydropyridine calcium channel blockers[31-33] (figure1).

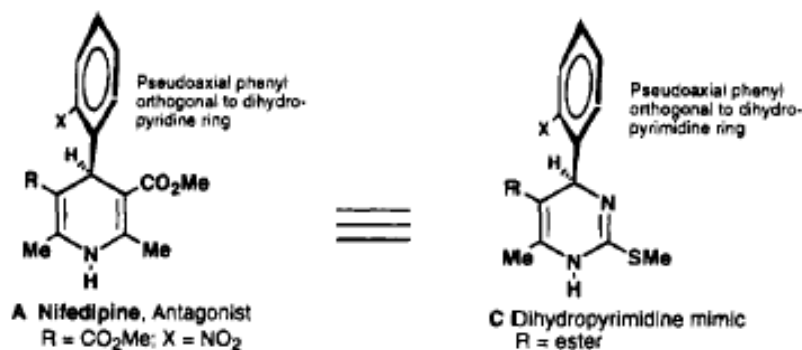


Figure 1

In 1995, a detailed structure-activity profile[34-35] for a series of dihydropyrimidine derivatives was reported, leading to a general binding site model for dihydropyrimidine/dihydropyridines as calcium channel modulators[36]. A normal vs. capsized DHP/DHPM boat model was proposed to explain structural and conformational requirements for modulation of calcium channel function. According to it, left-hand side alkoxy cis-carbonyl interaction with respect to C5=C6 bond is required for maximal DHP/DHPM receptor affinity and also the effect on channel function being determined by the absolute configuration at C4 whereby the orientation of the 4-aryl group (R- versus S-enantiomer) acts as a “molecular switch” between antagonist and agonist activity. It was proposed that in receptor bound conformation, the substituted aryl ring is positioned axially, perpendicular to, and bisecting the boat like dihydropyridine/dihydropyrimidine ring, with the 4-aryl substituent adopting a synperiplanar orientation relative to C4-H [37-40] (figure 2). Enantiomers having an up-oriented pseudoaxial aryl group (normal DHP/DHPM boat) will elicit calcium antagonist activity whereas enantiomers having a down-oriented pseudoaxial aryl group (capsized DHP/DHPM boat) will elicit calcium agonist activity (figure 2).

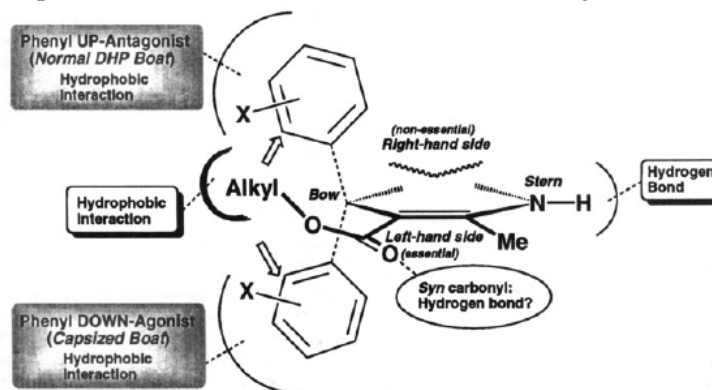
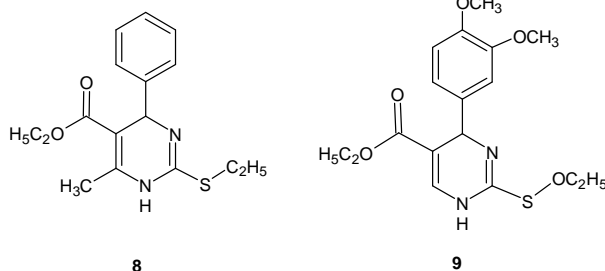


Figure 2

As a correlation has been observed between the pharmacological activity of this class of calcium channel antagonist and the magnitude at 1,4-dihydro ring puckering, the observed ring distortions were found to be influenced to a great extent by the position of substituent in the 4-phenyl ring and the inter ring bond [41]. In receptor bound conformation [42] it has been presented that the changes on right hand side(R.H.S.) of the molecule do not affect the activity and hence the substitution on the right hand side was termed non-essential. But contrary to the earlier [42] report it has been proved by our laboratory [43] that one cannot ignore the structural details at the right hand side also. These observations have increased our interest to synthesize some dihydropyrimidines that can act as valuable substitutes for Nifedipine. The changes were made in the substituents at position 2 and 5 of the pyrimidine ring. Kaur et al[58] synthesized various such

compounds with the aim of having improved activity and lesser toxicity compared with other calcium channel blockers in clinical use. Regarding this, two such compounds 6-methyl-4-phenyl-2-S-ethyl-1,4-dihydropyrimidin-5-carboxylic acid ethyl ester (8) and 6-methyl-4-(3,4-dimethoxy)phenyl-2-S-ethyl-1,4-dihydropyrimidin-5-carboxylic acid ethyl ester (9) has been synthesized and studied [58], to find out its biological effect and calcium channel blocking activity.



For evaluation of compounds 8 and 9, experiments were conducted on rat uterus, rabbit aorta, rabbit heart and frog heart

Rat Uterus: Rat uterus was used to quantify the inhibitory action of the test compound and to calculate IC_{50} in the present study. Priming was done 24 hours prior to every experiment, by administration of diethylstilbestrol (DES), 0.1 mg/kg body weight, subcutaneously. Dissection was done and preparation mounted in De Jalon solution as per the method described in literature [44]. KCl was added to the bath to get a final concentration of 60mM. Fine suspensions of the test compound in 1% carboxymethylcellulose (CMC) were then added in geometric doses. A cumulative dose response curve was obtained and IC_{50} (the molar dose which produces 50% relaxation is taken as IC_{50} , inhibitory concentration), calculated.

IC_{50} in Rat uterus for 8 is 1.2×10^{-5} M

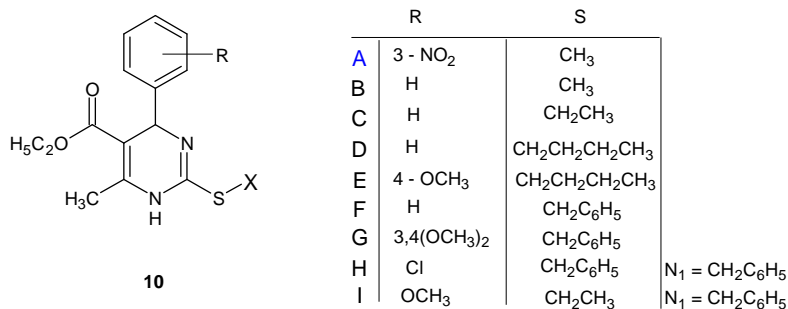
IC_{50} in Rat uterus for 9 is 3.98×10^{-5} M

Rabbit Aorta: To see the effect on rabbit aorta calcium induced contractions in depolarized arterial smooth muscles of rabbit isolated aortic strip were studied. Experiment was conducted as described in literature [45-46]. Aortic strips were then suspended in a 25 ml organ bath containing modified Krebs solution at $37^{\circ}C$ which was continuously oxygenated. The compound 8 produced statistically significant inhibition of Ca^{2+} induced contraction of K^{+} depolarized rabbit's aortic strip at all the bath concentrations. Thus, the compound 8 produces dose dependent relaxation of rabbit aorta strip. While the compound 9 produces statistically significant inhibition of rabbit aorta strip at bath concentration of 2.7×10^{-5} M only. Thus, dose dependent increase in relaxant effect was not observed in the case of 9. The rabbit heart was mounted as per the methods described by Burn [45] and Perry [46]. The heart was mounted in the Langendorff's assembly and perfused with Ringer Locke solution at $37^{\circ}C$. The effect of the test compounds on heart rate, amplitude and coronary flow was compared with vehicle alone. A comparison of mean percentage change with PG alone and the compound 8 (solution in PG) shows that it does not have any significant effect on Rabbit's heart rate. It also has no significant change in coronary flow of rabbit's heart. But in compound 8 significant to very significant decrease in the amplitude of contraction of heart was observed. The compound 9 also does not cause any significant alteration in heart rate, amplitude and coronary flow in rabbit heart.

Frog's Heart: The experiments were performed as described in literature [45] Frog's Ringer solution was used as a perfusion fluid at a rate of 45 drops min^{-1} . Sensitivity of heart was tested by administering adrenaline hydrochloride solution 2 mg. The effect of the test compounds in propylene glycol was observed regarding heart rate and amplitude. The compound 8 has a significant mean percentage decrease in heart rate from 1st to 5th minute with doses 0.1 ml, 0.2 ml and 0.4ml. There was also uniform significant to very significant dose dependent mean percentage decrease in amplitude, during the five minutes. While 9 produced significant decrease in heart rate at lower doses with higher doses there was no significant

change. Compound 8 also had a dose-dependent relaxant effect on intestinal smooth muscles of isolated rabbit intestine. Statistical significance of the differences between various groups, were analyzed using student's "t" test. P-values of <0.05 and <0.01 were taken statistically significant & highly significant respectively. A comparison of the mean percentage change with PG alone and 9 (solution in PG) shows that the compound 9 does not cause any significant alteration in heart rate, amplitude and coronary flow in rabbit heart. In the experiment of frog's heart in situ. The compound 9 produced significant decrease in heart rate and amplitude i.e. it decreases the force of contraction of heart, which is the property of calcium channel blockers. Thus it can be concluded that compound 9 does possess calcium channel blocking activity and it has significant dose dependent relaxant effect on aortic smooth muscles also but dose dependent increase in relaxant effect was not observed. The compound 9 has significant chronotropic and negative inotropic effects on frog's heart in situ at low doses. The other compounds of this series have also shown calcium blocking activity of variable potencies. The results obtained for compound 8 are summarized below:

Compound 8 does have a calcium channel blocking activity and it had a dose-dependent relaxant effect on the intestinal, uterine and aortic smooth muscles. Compound 8 had a significant negative chronotropic effect in frog's heart but no significant effect on Rabbit's heart rate. Compound 8 had a significant dose dependent negative inotropic effect on both mammalian and amphibian hearts. The compound 8 had no significant change in coronary flow of Rabbit's heart. Thus it can be concluded that compound that compound 6-methyl-4-phenyl-2-S-ethyl-1,4-dihydropyrimidin-5-carboxylic ethyl ester activity which was dose related on various tissue preparations. Also, Rana et al[47] have carried out potent Ca^{2+} channel antagonistic activity of 2-S-alkyl-1,4-dihydropyrimidine and 2-S-Benzyl-1-N-Benzyl-1,4-dihydropyrimidines, after their synthesis. Female albino rats of Wistar strain were sacrificed by stunning and the uterine horns were excised and mounted in an organ bath. KCl induced contraction of isolated rat uterus were recorded using frontal writing lever on a benzene in 1% carboxymethyl cellulose and was added to bath in geometric doses so as to obtain a cumulative dose response curve (DRC) and IC_{50} for each test compound. At least six DRC were plotted for each compound. The mean $\text{IC}_{50} \pm \text{SEM}$ was calculated for each compound. The following compounds have shown different potency for Ca^{2+} channel antagonistic activity.



S-ethyl derivative (c) is the most potent calcium channel blocker as it has the lowest IC_{50} value given in table 1.

Table 1. IC_{50} value of compound 10 (a-i)

Compounds	F.Wt.	IC_{50}
10 a	351	6.40
10 b	306	6.70
10 c	304	4.4
10 d	332	15.3
10 e	362	9.35
10 f	366	13.5

10 g	426	18.5
10 h	490	235.0
10 i	484	1870.12

PASS Method [48] for Biological Activity Studies: Another method to determine the physiological activity is through a software called PASS. This is being done by SPECS and BioSPECS. PASS is a software application that predicts 435 possible biological activities of a user-selected (set of) compounds (s). These activities include 5-hydroxytryptamine antagonists, neuromuscular blocking agents, antibiotics, antidepressants, antiviral agents (AIDS), contraceptives, tumor necrosis factor antagonists and many others. The PASS training set consists of 16,000 known drugs and 15,000 compounds that are in clinical or advanced pre-clinical trials.

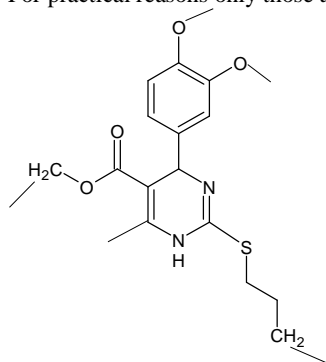
Interpretation of data: The PASS algorithm produces a list of biological activities for which the calculated probability to be active (P_a) is higher than calculated probability to be inactive (P_i). In general a higher P_a value can be interpreted as a higher probability of finding activity in a bio-assay accompanied by a higher probability of being a close analogue to one of the compounds that were used in the PASS training set. The table 2 gives an overview of the different P_a intervals and their attributed probabilities.

Table 2

Generated P_a -value	Probability of finding activity in bio-assay	Probability of being a close analogue of a known drug	Probability of being a new chemical entity (N_c)
$P_a > 0.9$	High	High	Low
$0.7 < P_a < 0.9$	Moderate	Moderate	Low-Moderate
$0.5 < P_a < 0.7$	Moderate-low	Moderate-low	Moderate
$P_a < 0.5$	Low	Low	High

PASS also calculates a number of substructure descriptors and will also present the number of new descriptors i.e. the number of substructure not used in the training set. If this number is larger than three, the reliability of the prediction is low.

For practical reasons only those activities will be listed for which $P_a - P_i > 0.5$.



ID NUMBER AQ - 141/41076216

M.Wt: 392.5212

 $C_{20}H_{28}N_2O_4S$

Activity Prediction:

51 Substructure descriptors: 0 new.

52 Possible activities at $P_a > P_i$.

P_a P_i for Activity

0.585 0.005 Calcium channel antagonist

0.573 0.089 Atherosclerosis treatment

0.465 0.046 Antianginal

0.419 0.017 Thrombolytic

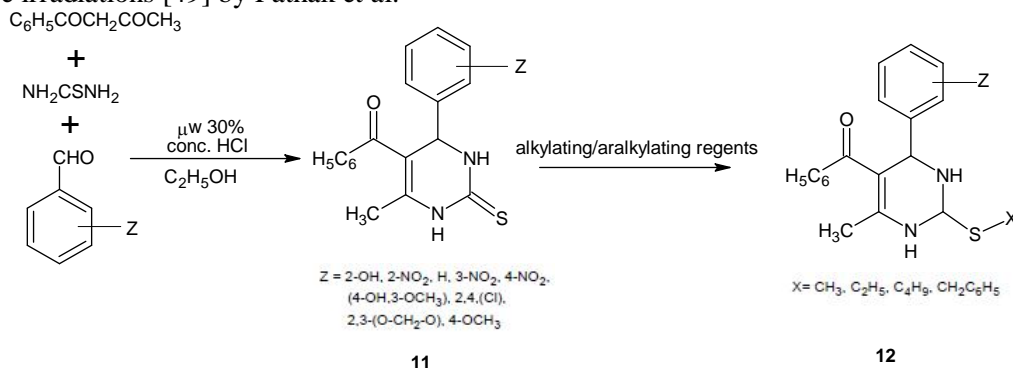
0.420 0.027 Adenosine A3 receptor antagonist

0.433 0.055 Antihypertensive

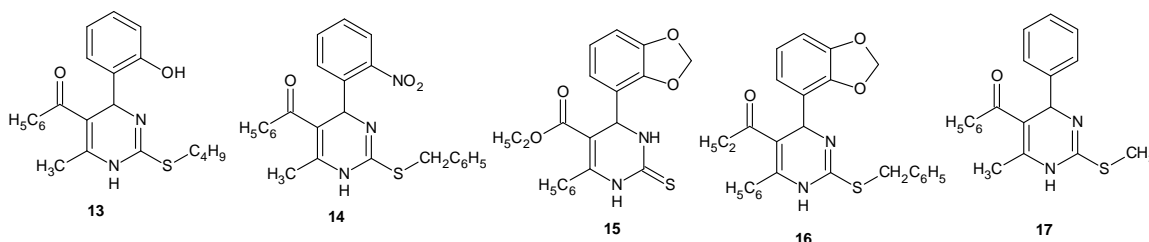
0.426 0.048 Leukopoiesis inhibitor

0.428	0.063	Antiulcerative
0.361	0.024	Anti-Helicobacter pylori
0.296	0.035	Gastric antisecretory
0.281	0.052	Glucagon receptor antagonist
0.332	0.104	HDL-cholesterol increasing
0.198	0.019	Thyroid hormone antagonist
0.276	0.101	Spasmolytic, Papaverin-like
0.278	0.112	Ophthalmic drug

The acid catalysed condensation of aromatic aldehyde, benzoyl acetone and thiourea was carried out microwave irradiations [49] by Pathak et al.



The biological activity of the following compounds were carried out. For this, experiments were conducted on rat uterus and rabbit heart [50].



Rat Uterus: Female albino rats were used[45]. Diethyl stilbesterol 0.2 mg kg⁻¹ body weight was administered to rats subcutaneously. Fine suspensions of test compound in 1% carboxy methyl cellulose were added in geometric doses. A cumulative response curve was obtained and IC₅₀ was calculated. The molar dose which produces 50% relaxation is taken as IC₅₀ (Inhibitory concentration). The compounds 13 to 17 were found to have a dose dependent relaxant effect on K⁺ induced contractions of isolated rat uterus with IC₅₀ as follows:

1. IC₅₀ in rat uterus for compound 13 is 0.74 X 10⁻⁴ M (28 mg ml⁻¹).
2. IC₅₀ in rat uterus for compound 14 is 0.52 X 10⁻⁴ M (22 mg ml⁻¹).
3. IC₅₀ in rat uterus for compound 15 is 1.38 X 10⁻⁴ M (47 mg ml⁻¹).
4. IC₅₀ in rat uterus for compound 16 is 1.17 X 10⁻⁴ M (54 mg ml⁻¹).
5. IC₅₀ in rat uterus for compound 17 is 0.53 X 10⁻⁴ M (17 mg ml⁻¹).

Rabbit Heart: The rabbit heart was mounted as per methods described [45-46]. The heart was mounted in Langedoff's assembly and perfused with oxygenated Ringer Locke solution at 37°C. The effect on coronary flow and amplitude in rabbit heart was studied. The compounds 13 to 17 show increase in coronary flow at all doses. There was also increase in amplitude except there was decrease in amplitude in 16 at dose of 80 mg/ml. As these compounds cause increase in coronary flow as well as increase in amplitude, these compounds can be useful in conditions like Congestive heart failure (CHF) while, other Ca²⁺ channel blockers like Nifedipine, decrease the force of contraction of heart so cannot be useful in

such conditions. The same property appears in commonly known drug “digoxin” which is largely used by the patients of Congestive heart failure. These compounds may be useful in CHF but further studies are needed not only in animal and tissue models but also in various pathophysiological models. The results of all the experiments has shown that compounds 13 to 17 were found to have relaxing effect on the K⁺ induced contractions of isolated rat uterus. Thus all these compounds show smooth muscle relaxing property like that of known calcium channel blockers.

ANTIBACTERIAL ACTIVITY

Evaluation of anti-bacterial activity of some of the prepared Quinazoline and Pyrimidine was carried out. *In vitro* antibacterial activity of the different compounds was studied against seven bacterial strains (Pseudomonas fluorescence 103, Staphylococcus aureus 1740, Acinetobacter sp.127, Bacillus subtilis 2451, Staphylococcus epidermis 435, Salmonella typhimurium TA 98 1251, Escherichia coli) by the agar well diffusion method as described by Perez *et al.*, 1990[51] with certain modifications. Nutrient agar (Hi Media, India) was used as the bacteriological medium. The antibacterial activity of different compounds was taken at different concentrations (500 and 250 µg well⁻¹). The nutrient agar was melted and cooled to 48-50°C and a standardized inoculum of 1×10^6 CFU ml⁻¹ was then added aseptically to the molten agar and poured into sterile Petri dishes to give a solid plate. Wells were prepared in the seeded agar plates. The test compound was introduced in the well (8.5 mm). The plates were incubated overnight at 37 °C. The antimicrobial spectrum of the compounds was determined for the bacterial species in terms of zone sizes around each well. The diameters of zone of inhibition produced by the agent were compared with those produced by the commercial control antibiotics, Amoxicillin (5 mg/ml) and Ciprofloxacin (5 mg ml⁻¹). The experiment was performed three times to minimize the error and the mean values are presented.

A. The biological activity of the following Pyrimidine derivatives (table 3) were carried out [52].

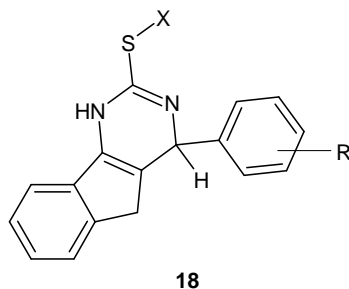


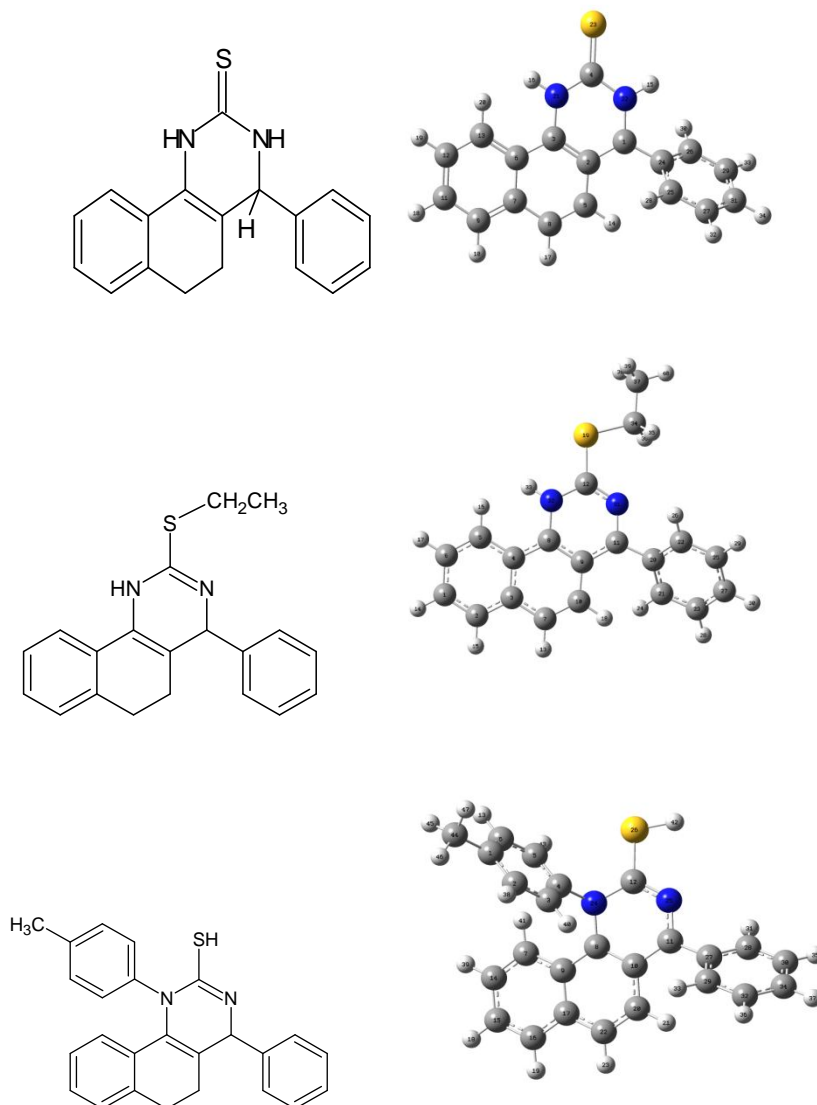
Table 3

Compound No.	R	X
18 a ; 18b	2,4-Cl	C_2H_5 ; CH_3
18 c; 18d	4-NO ₂	CH_2CH_2 ; CH_3
18 e ; 18f; 18g	4-OCH ₃	CH_3 ; $CH_2CH_2CH_2CH_2$, C_2H_5
18 h; 18i	H	C_2H_5 ; CH_2CH_2
18 j; 18k; 18l; 18m	2,3(O-CH ₂ -O)	C_2H_5 ; $CH_2CH_2CH_2CH_2$, CH_3 , CH_2CH_2
18 n; 18o	4-OH,3-OCH ₃	CH_3 ; C_2H_5
18 p; 18q; 18r; 18s	3-NO ₂	$CH_2CH_2CH_2CH_2$; CH_3 , C_2H_5 , CH_2CH_2
18 t; 18u	2-CH ₃	C_2H_5 ; CH_3

This means that the S-Me or S-Et derivatives synthesized from vanillin are much more potent than other derivatives for anti-bacterial activities. Once again, it was verified from the results discussed, that right hand side cannot be neglected in receptor bound theory.

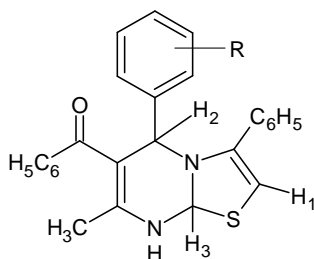
COMPUTATIONAL STUDIES

As shown by the Gaussian 03 studies through the computer, the stereochemistry of the synthesized compounds seems to be like the reported compounds in the literature[22,54,55].



Bansal et al [56-57] synthesized pyrimidine derivatives by reacting thiazole with benzoyl acetone/ ethylacetoacetate and aromatic aldehydes under microwave irradiation. Antimicrobial activity of [5-(substitutedphenyl)-7-methyl-3-phenyl-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidin-6-yl](phenyl)methanone derivatives were carried out. For this, Gentamycin and were used as the standard and add compounds were screened for their antibacterial activity against *Staphylococcus aureus*, *Staphylococcus aureus* (MRSA), *Staphylococcus pyogenes* according to the Agar Diffusion Method using dimethylsulfoxide as solvent. The test compounds used for antifungal screening were *Aspergillus niger*, *Neurospora crassa*. In general, compounds exert very low antibacterial activity but moderate to good antifungal activity. All tested compounds show more activity towards *S. Pyrogens* as compared to other

bacterial strains. For this, compound 4n shows maximum activity. For strain *Neurospora crassa*, tested compounds show MIC value equal to or even less than the standard drug. In general, 21d and 21n show good results.



21

Product	R
21a	H
21b	4-OCH ₃
21c	2-NO ₂
21d	4-(OH),3-(OCH ₃)
21e	3-OH
21f	2,3-(O-CH ₂ -O)
21g	4-NO ₂
21h	2,4-(Cl)
21i	3-NO ₂
21j	2-Cl
21k	3,4()
21l	4[4-{N(CH ₃) ₂ }]
21m	2-OH
21n	4-OH

APPLICATIONS

Thiols of pyrimidine and quinazoline can act as anti-convulsive drugs comparable to important drug phenobarbitone. The discussed compounds can act as good antimicrobial activities.

CONCLUSIONS

Some important conclusions can be made from this review. Thiols of pyrimidine and quinazoline can act as anti-convulsive drugs comparable to important drug phenobarbitone. On comparing S-methyl/ethyl derivative of 1, 4-dihydropyrimidine with Nifedipine, it has been found that it is most potent and S-methyl/ethyl moiety is present on right side of the boat shaped conformation. This shows that one cannot ignore the structural details at right hand side as reported earlier. Substitution with 2-NO₂, 2-OH in aromatic ring also changes biological activity. When benzoyl group was substituted at position 5; it increased the force of contraction of heart, which made these compounds useful in congestive heart failure conditions. Besides this, the discussed compounds can act as good antimicrobial agents.

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