International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 5 Issue 6, June 2018

ISSN: 2394-4404

Pharmacological Potential Of 1,3,4-Thiadiazole Moiety – A Review

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Abstract: ***Several thiadiazole derivatives were synthesized and their diverse biological activities have been studied over the years. Of these thiadiazole derivatives, 1,3,4-thiadiazole has proved to be a promising moiety in the novel drug development. They were synthesized by the cyclisation of various acylhydrazines and thiohydrazines. The derivatives disclose a number of biological activities such as antioxidant, anticancer, anti-inflammatory activities. This review is intended to study the synthesis, chemistry and biological activities of 1,3,4-thiadiazole derivatives.***

Keywords: 1,3,4-thiadiazole, anticancer, antimicrobial, anti-inflammatory.

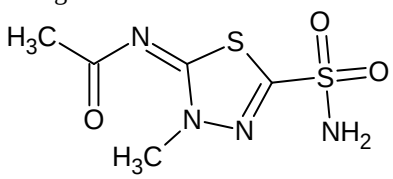
I. INTRODUCTION

Heterocyclic compounds have exhibited considerable significance in novel drug design. Compounds having five membered heterocyclic ring systems such as thiazole, oxazole, imidazole, oxadiazole and thiadiazole have demonstrated numerous bioactivities. Thiadiazole is a chemical moiety that contains two nitrogen atoms and one sulfur atom as heteroatoms. Thiadiazole ring exists in four isomeric forms which are 1,2,3-thiadiazole, 1,2,4,-thiadiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole. 1,3,4-thiadiazole, a fascinating pharmacophore, is a weak base because of the inductive effect exerted by the sulfur atom and possess relatively high aromaticity. Of these four isomeric forms 1,3,4-thiadiazole have displayed a broad spectrum of biological activities such as antimicrobial, anticancer, diuretic, antioxidant, anticonvulsant and anti-inflammatory activity[(2)].

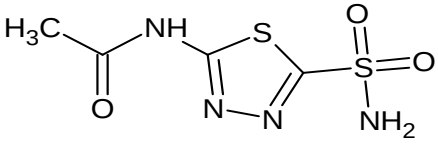
1,2,3 - thiadiazole 1,2,4 - thiadiazole 1,2,5 - thiadiazole 1,3,4 - thiadiazole

Figure 1: Isomeric forms of thiadiazole ring

Number of drugs currently available in the market having 1,3,4-thiadiazole nucleus are: methazolamide and acetazolamide, diuretics that exert their action by inhibition of the enzyme carbonic anhydrase. Some other drugs of the same moiety are megazol, an antiparasitic drug and first-generation cephalosporins, cefazolin and cefazedone and azetepa an antineoplastic drug.



Methazolamide



Acetazolamide

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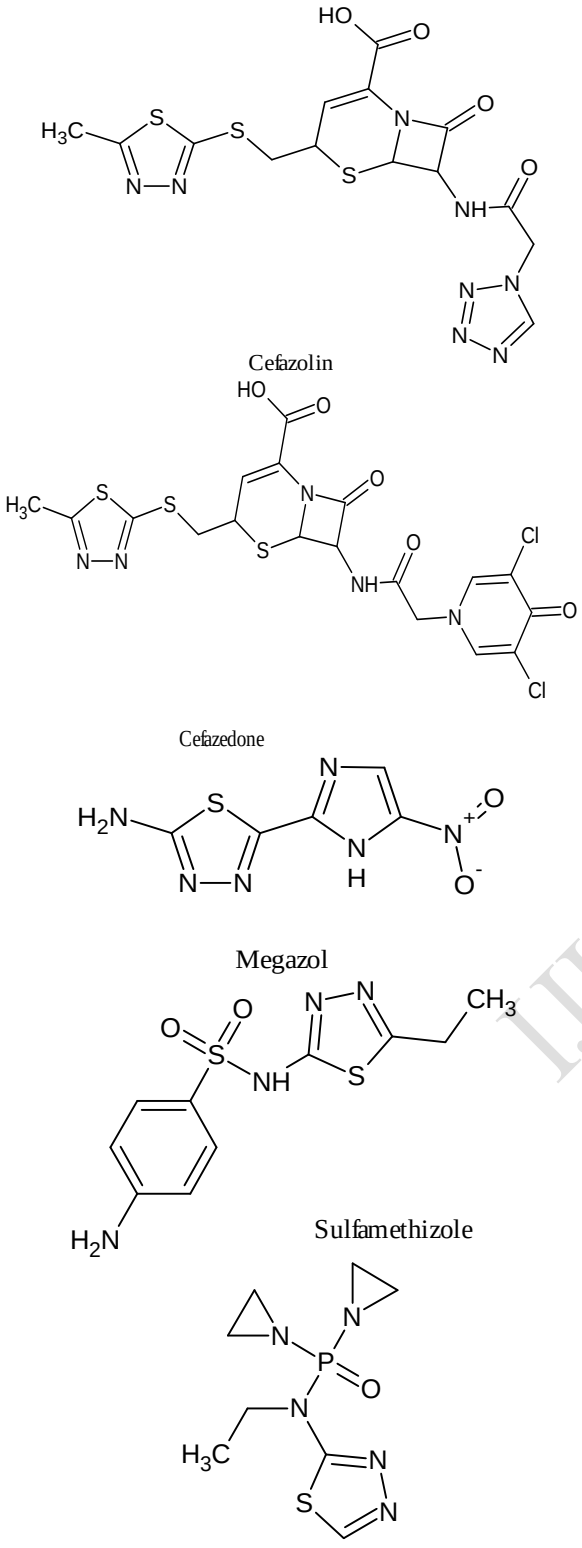

Figure 2: Drugs containing 1,3,4-thiadiazole ring

II. SYNTHESIS OF 1,3,4-THIADIAZOLE

1,3,4-thiadiazole derivatives are mainly synthesized from acylhydrazines and thiohydrazines. The cyclization of acylhydrazines gives 1,3,4-thiadiazole. The commonly used acylhydrazines are N,N'-diacylhyrazines and monoacylhydrazines. The thiohydrazines used for the synthesis of 1,3,4-thiadiazole are thiosemicarbazide, thiocarbazide, bithioureas, dithiocarbazates, and thioacylhydrazines.

A. FROM ACYLHYDRAZINES

The synthesis of 1,3,4-thiadiazole from acylhydrazines is mainly by the sulfuration of the acylhydrazines using phosphorous sulfide reagents like P_2S_5 and Lawesson's reagent. But these methods have the disadvantages of formation of intractable byproducts and need a lot of hard conditions for the synthesis of 1,3,4-thiadiazole derivatives.

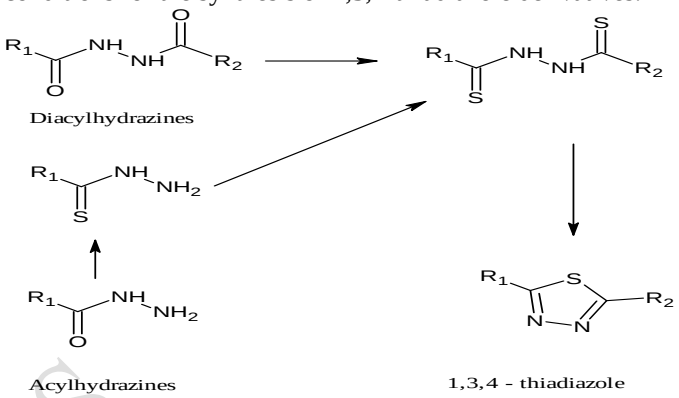

Figure 3: Scheme for the general preparation of 1,3,4-thiadiazole from acylhydrazines

In acylhydrazines, acid hydrazides and carboxylic acids are used for the synthesis of 1,3,4-thiadiazole derivatives. In this synthetic method 1,3,4-thiadiazole derivatives are prepared by the reaction of carboxylic acid with propylphosphonic anhydride. The propylphosphonic anhydride (T_3P) plays a role as coupling and cyclodehyration reagent.

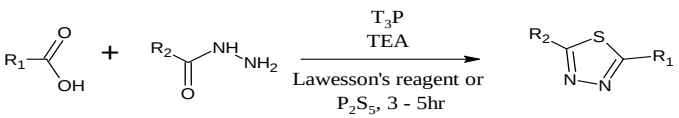

Figure 4: Scheme for the preparation of 1,3,4-thiadiazole from carboxylic acid

By using microwave irradiation method 1,3,4-thiadiazole derivatives are prepared from acid hydrazides. Aromatic and heterocyclic hydrazides are allowed to react with triethyl orthoformate, triethyl orthopropionate and triethyl orthobenzoate. This reaction is catalyzed by solid supported NafionNR50 and thionating agent phosphorus pentasulfide in alumina.

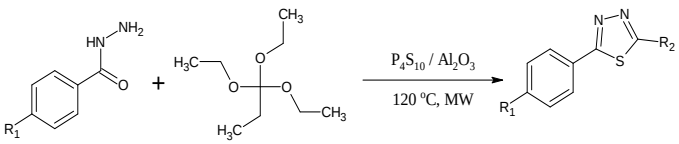

Figure 5: Scheme for the preparation of 1,3,4-thiadiazole from acid hydrazides

Synthesis of 1,3,4-thiadiazole is also performed by using N,N'-diacylhydrazines. The N,N'-diacylhydrazines undergo cyclization with phosphorous sulfides such as P_2S_5 and Lawesson's reagent in solvents like DMF, dioxane, THF gives 1,3,4-thiadiazole derivatives.

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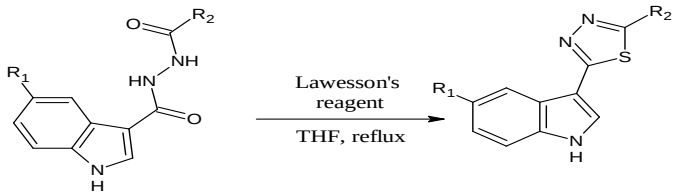

Figure 6: Scheme for the preparation of 1,3,4-thiadiazole from diacylhydrazines

B. FROM THIOHYDRAZINES

The widely used method for the synthesis of 1,3,4-thiadiazole is from thiosemicarbazide or substituted thiosemicarbazide. The cyclisation of thiosemicarbazide or substituted thiosemicarbazide gives 2-amino-1,3,4-thiadiazole derivatives. 2-amino-1,3,4-thiadiazole derivatives are prepared by the reaction of carboxylic acid with thiosemicarbazide in the presence of an ionic liquid. By this method both mono and bicyclic 2-amino-1,3,4-thiadiazole derivatives can be synthesized.

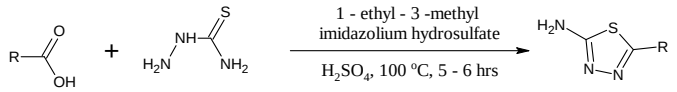

Figure 7: Scheme for the preparation of 1,3,4-thiadiazole from thiosemicarbazide

Another thiohydrazine is thiocarbazide which is also known as carbonothioic dihydrazide used for the synthesis of 1,3,4-thiadiazole derivatives by the same mechanism with that of thiosemicarbazide. Thiosemicarbazide gives 2-amino-1,3,4-thiadiazole derivatives where thiocarbazide gives 2-acylhydrazine-1,3,4-thiadiazole derivatives. Reaction of thiocarbazide with appropriate hydrazonoyl halide yield corresponding 1,3,4-thiadiazole derivatives.

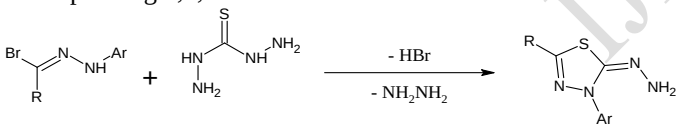

Figure 8: Scheme for the preparation of 1,3,4-thiadiazole from thiocarbazide

Dithiocarbazate is a thiohydrazine which is used for the synthesis of 1,3,4-thiadiazole. The acylation of dithiocarbazate with chloroacetylchloride followed by the dehydration gives corresponding 1,3,4-thiadiazole derivative.

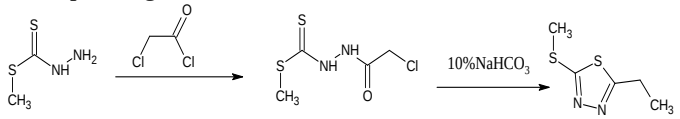

Figure 9: Scheme for the preparation of 1,3,4-thiadiazole from dithiocarbazate

III. PHARMACOLOGICAL ACTIVITIES OF 1,3,4-THIADIAZOLE

Many drugs are available in the market with 1,3,4-thiadiazole nucleus. 1,3,4-thiadiazole derivatives possess wide range of biological activities like antimicrobial activity, anti inflammatory activity, antitumor activity, anticonvulsant activity and diuretic activity.

A. ANTIOXIDANT ACTIVITY

Antioxidants eradicate the free radical intermediates from oxidation reactions thus preventing oxidative damage and death of the cells. N-(2,4-Dimethylphenyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine exhibited greater superoxide anion scavenging activity than the reference standard propyl gallate. Various (benzo)-imidazothiadiazoles and triazolothiadiazoles are compounds with significant antioxidant activity against various in vitro systems such as 2,2-diphenyl-1-picrylhydrazyl radical, superoxide radical, microsomal NADPH-dependent inhibition of lipid peroxidation (LP) levels and nitric oxide scavenging activity.

B. ANTI INFLAMMATORY ACTIVITY

Numerous non steroidal anti-inflammatory (NSAIDs) drugs are used as analgesic, antipyretic and anti-inflammatory agents. The COOH group in the NSAIDs is reported to be responsible for the anti-inflammatory activity. However some derivatives also show anti-inflammatory activity in the absence of COOH group which is replaced by the thiadiazole ring. Amir et al performed a characteristic change in the structure of the standard drug naproxen. The COOH group in naproxen was replaced by the N-(4-bromophenyl)-1,3,4-thiadiazol-2-amine gave compound (1) that retained almost equal anti-inflammatory activity as naproxen. They also designed indomethacin derivatives by the replacement of COOH group with substituted amino-1,3,4-thiadiazole moiety gives compound (2) shows significant anti-inflammatory and analgesic activity.

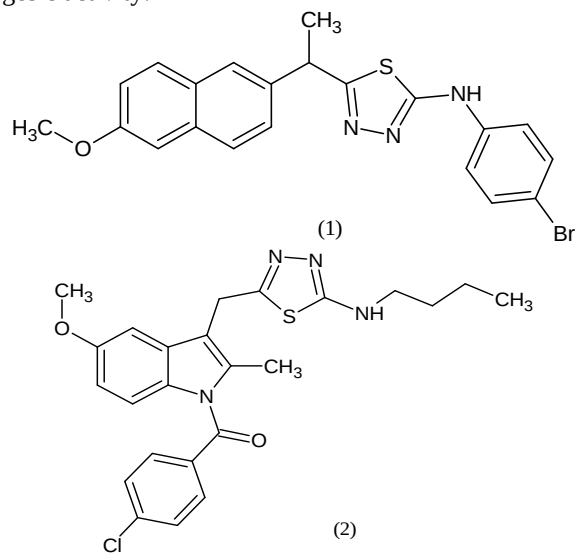

Figure 10: 1,3,4-thiadiazole derivatives exhibiting anti-inflammatory and analgesic activity

Schenone et al synthesized a group of N-[-5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides and determined for their anti-inflammatory activity. The benzoyl sulfonamido series showed good activity. Among them compound (3a) and (3b) were the most active compound.

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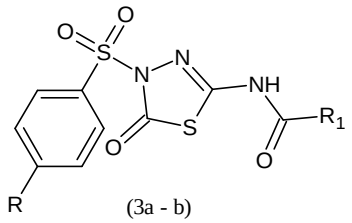


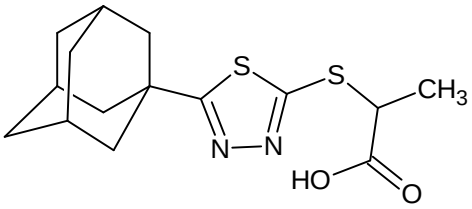
(3a - b)

3a = R = H; R_1 = 4 - $CF_3CH_2C_6H_4$

3b = R = H; R_1 = 4 - FC_6H_4

Figure 11: 1,3,4-thiadiazole derivatives exhibiting anti-inflammatory activity

Kadi et al evaluated new series of 5-(1-adamantyl)-1,3,4-thiadiazole(4) derivatives for their anti-inflammatory activity. Derivative substituted with propionic acid at 2nd position of 1,3,4-thiadiazoline-2-thiones, exhibit almost equal anti-inflammatory activity at 20 mg/kg to that of Indomethacin (5 mg/kg).

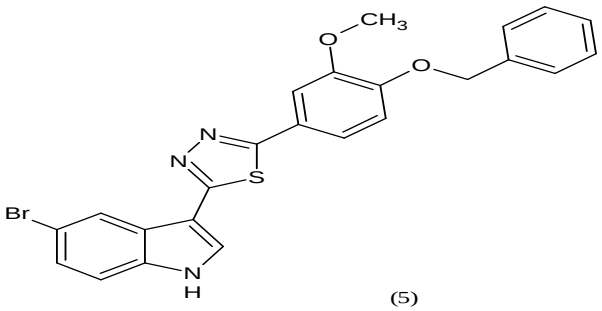


(4)

Figure 12: 5-(1-adamantyl)-1,3,4-thiadiazole derivative having anti-inflammatory activity

C. ANTICANCER ACTIVITY

The compound with substitution on C-2 position of the 1,3,4-thiadiazole ring plays an important role in exhibiting the cytotoxic activity. Replacement of phenyl group at C-2 position with benzyl, 4-(dimethylamino) phenyl, 3,4-dimethoxyphenyl and 4-benzyloxy group increased the antineoplastic activity. Compound (5) with 4-benzyloxy-3-methoxyphenyl at C-2 position and 5-bromoindole at C-5 position was found to be the most potent compound of the series.



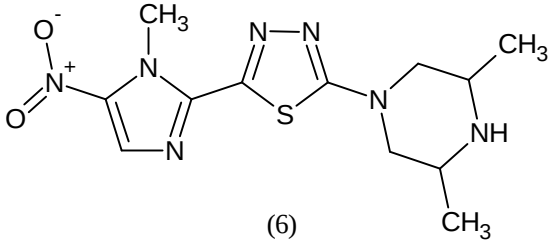
(5)

Figure 13: 1,3,4-thiadiazole derivative exhibiting anticancer activity

D. ANTIMICROBIAL ACTIVITY

Approximately all of the existing 1,3,4-thiadiazole derivatives exhibit greater antibacterial activity against Gram positive bacteria than Gram negative bacteria because of their differences in the structure of cell wall.

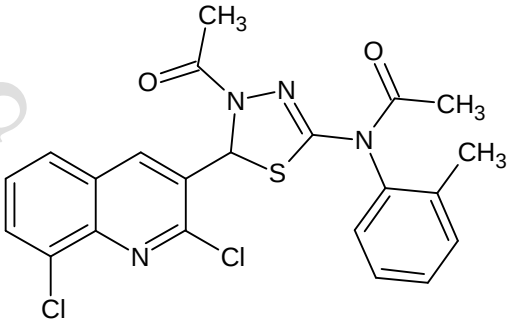
There are numerous compounds bearing the thiadiazole ring that possess excellent antimicrobial activities. Several 1,3,4-thiadiazoles synthesized by Moshafi et al. were evaluated for antibacterial activity against *Helicobacter pylori* in a disc diffusion test at 0.5 mg/disc. At this dose, compound 6 gave a zone of inhibition of 30.9 mm in diameter, five times greater than that observed for the positive control metronidazole (6 mm).



(6)

Figure 14: 1,3,4-thiadiazole derivative exhibiting anti H.pylori activity

1,3,4-thiadiazole ring system that exhibits wide spectrum of antimicrobial activity. It has shown improved activity when attached with various chemical moieties such as quinoline and triazole.



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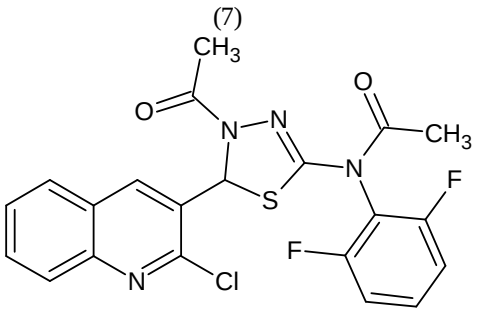

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Figure 15: 1,3,4-thiadiazole derivative having antibacterial activity

Hybrids of 1,3,4-thiadiazole and different quinolones such as ciprofloxacin, norfloxacin, gatifloxacin exhibited 30-60 fold higher antibacterial activity than parent fluoroquinolones against Gram positive bacteria.

A number of 1,3,4-thiadiazole derivatives revealed antitubercular activity. Various 1,3,4-thiadiazoles (Ar = 5-nitro-2-furyl, nitroimidazolyl and 5-nitro-2-thienyl; n = 0-2) exhibit antitubercular activity.

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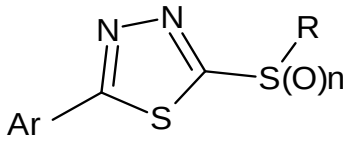


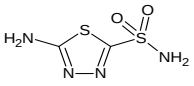
(9)

Figure 16: 1,3,4-thiadiazole derivative having anti tubercular activity

In general 1,3,4-thiadiazole derivatives have been reported to be less active against fungi.

E. CARBONIC ANHYDRASE INHIBITORS

The sulfamide group of sulfonamides is similar to the carbonate ion and can competitively inhibit carbonic anhydrases (CAs). Compounds containing a thiadiazole should also possess high inhibitory activity when bonded with a sulfamide group. From compound 10, some of the most widely used CA inhibitors were obtained, among which acetazolamide is the most potent inhibitor. Ilies et al. synthesized and evaluated several sulfonamides as inhibitors of CA. The affinity of compound 11 for CA increases significantly when substituted with sulfonamides 12 connected with 1,3,4-thiadiazole derivative. These results indicate that the thiadiazole ring has advantages over benzene in the context of CA inhibition.



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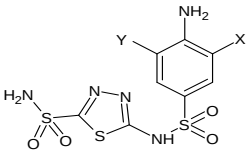

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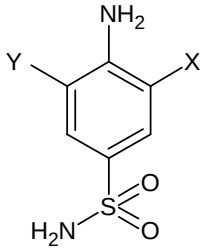
X = F, Cl, Br,

Y = Cl, Br, I



X = F, Cl, Br,

Y = Cl, Br, I

(12)

Figure 17: 1,3,4-thiadiazole derivatives exhibiting carbonic anhydrases inhibition

IV. CONCLUSION

1,3,4- thiadiazole possess various types of pharmacological acivities. When the COOH group of NSAID, naproxen is replaced with 1,3,4- thiadiazole derivative anti-inflammatory activity is retained. When the COOH group of indomethacin is replaced by 1,3,4-thiadiazole ring its activity was greater than the parent indomethacin. The 1,3,4-thiadiazole nucleus possess anticancer activity. The replacement of phenyl ring at C-2 position with 4-benzyloxy group and 5-bromo indole substitution at C-5 increased the anticancer activity. The 1,3,4-thiadiazole ring system exhibits significant antimicrobial activity. The 1,3,4-thiadiazole derivative possess more antimicrobial activity than standard drug metronidazole against *H.pylori*. The potent carbonic anhydrase inhibitor acetazolamide contains 1,3,4-thiadiazole nucleus. Hence 1,3,4-thiadiazole scaffold has potential for the design of wide spectrum of novel pharmacological agents.

ACKNOWLEDGEMENT

The authors are thankful to the Management and Principal of St James College of Pharmaceutical Sciences, Chalakudy, Kerala for providing the facilities to accomplish this review.

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