Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 1334-1341 | ISSN:2251-6727

Investigation on Synthesis and Etymology of Antifungal Action of Triazole Compounds by Coupling of Pyrimidine with Hydrazine Carbothioamide

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(Received: 16 July 2025 Revised: 20 August 2025 Accepted: 20 September 2025)

KEYWORDS

Pyrimidine, Triazole, Hydrazine carbothioamide, Antifungal activity

ABSTRACT:

Sequences of triazole-included pyrimidine compounds were synthesized via a multi-step process under mild and convenient conditions, affording reasonable to high yields. The structures of the synthesized selected compounds were confirmed by elemental analysis, GC-MS, ^{1}H and ^{13}C NMR, FT-IR, and CHN analysis. Further, biological assessment revealed that most of the compounds unveiled prominent antifungal activity, with compounds **3a** and **3g** demonstrating the most promising inhibition, comparable to the standard drug *Amphotericin-B*. This kind of biological active antifungal action of triazole compounds have wide potential applications in medical environment.

INTRODUCTION

The therapeutic properties of pyrimidine derivatives have generated a lot of interest. Because of the wide range of intriguing biological actions that have been noted for these compounds, including anticancer, antiviral, antitumor, anti-inflammatory, and antibacterial properties, pyrimidine derivatives [1-6] and substituted pyrimidine derivatives [7–13] continue to get attention. Strong C-C bond-forming agents, pyrimidine derivatives were used in a variety of ways to produce various amino-substituted derivatives [14-17]. A condensation process occurs between the primary or secondary amine, benzaldehyde and one or more active hydrogen atoms.

Additionally, ATP (adenosine triphosphate) analogues of pyrimidine and fused heterocyclic pyrimidine derivatives were well known for their potential biological activity [18], including antitumor [19], antimicrobial fungicide [20], algaecide and antibiotics [21-23]. Furthermore, their enormous synthetic potential was resolved by the presence of many interacting functional groups [24-28]. As part of this work, we synthesized 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenylpyrimidin-2(1*H*)-one (3a) and investigated its antifungal efficacy against

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JCHR (2025) 15(5), 1334-1341 | ISSN:2251-6727

Aspergillus Niger, Penicillium species and Candida albicans in vitro. The standard medication used was amphotericin-B.

According to literature procedure [1-2], the Biginelli reaction of aromatic aldehydes, ethylacetoacetate, and thiourea or urea was used to create the heterocyclic precursors DHPMs 1a–j, which were then used to create the aforementioned derivatives. Compounds 2a–j were then synthesised using these DHPMs. Mass spectra, ^{1}H and ^{13}C NMR spectrum analyses and elemental analysis were used to characterise each of the synthesised substances.

MATERIALS AND METHODS

All chemicals were purchased from Merck, India. Melting points were determined using the open capillary method and are uncorrected. The compounds were checked for homogeneity by TLC on Silica gel-G using Pet Ether and ethyl acetate in 3:5 ratio. The IR spectra were recorded on an FT-IR Thermo Nicolet Avatar 370 spectrophotometer using the KBr disc method. The ^{1}H and ^{13}CNMR were recorded on a Bruker Avance-III 400MHz FTNMR spectrophotometer using a 400MHz DMSO-d_6. Elemental analyses were recorded on Elemental Vario EL III. The mass spectra were recorded on a Joel GC-mate spectrometer. All compounds gave satisfactory micro-analytical results. Pyrimidine **1a** was prepared by the reported method [1-2].

Antifungal assay

The conventional agar well diffusion method was used for the antifungal analysis. Brain Heart Infusion (BHI) broth was used to suspend each bacterial isolate, which was then diluted to about 105 colony forming units (CFU) per milliliter. After being flood-inoculated onto the BHI agar surface, they were allowed to dry. A sterile cork-borer was used to cut five-millimeter-diameter wells out of the agar, and 30 µL (5µg compound in 500 µL DMSO) of the sample solution was added to the wells of Aspergillus Niger, Penicillium species and Candida albicans in mm against the test microorganisms. The solvent control was DMSO. The reference antifungal agent was amphotericin-B. The tests were carried out in triplicates.

Brain Heart Infusion (BHI) Agar-Composition

Composition: One liter of distilled water was used to suspend the 200g of calf brains (infusion) 12.5, 250g of beef heart (infusion) 5.0g, protease peptone 10.0, sodium chloride 5.0, D(+) glucose 2.0, sodium hydrogen phosphate 2.5g, agar 10.0g and final pH 7.4 +/- 0.2 at 37^0C. After the medium was fully dissolved by boiling, it was distributed into tubes, plates or flasks and autoclaved for 15 minutes prepared 121^0 C to sterilize. It was tightly sealed in containers at between 2 and 25^0C and protects the containers from direct sunlight.

General Procedure

The synthesis of 5-(hydrazine carbothioamide)-3, 4-dihydro-6-methyl-4-phenylpyrimidin-2(1*H*)-one **2a-j**, an equimolar mixture of compound **1**a (2.61g, 0.01 mol) and hydrazine carbothioamide (0.91g, 0.01 mol) in acetone was refluxed for 10–12 hours and allowed to cool and the yellow crude solid was purified by recrystallization from alcohol. m.p 139-141°C. Yield 2.4g (80%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 2.251 (s, 3H), 5.152 (d, $^{3}J_{HH}$ = 3.2Hz,1H), 6.501 (s, 2H), 7.213–7.336 (m, 5H), 7.702 (d, $^{3}J_{HH}$ = 2.8Hz, 1H), 8.175 (d, $^{4}J_{HH}$ = 6.4Hz, 2H,), 9.149 (s, 1H); ^{13}CNMR (400 MHz, DMSO-d_6) δ 17.72, 59.17, 99.33, 126.21, 127.23, 128.34, 148.25, 151.71, 152.16, 165.33, 178.40; FT-IR (KBr) ŭ 3365, 3241, 3116 (NH), 3079 (Ar-H), 2978 (CH), 1724 (C=O), 1385 (C-N), 1219 (C=S), 1089 (N-N) cm^{-1}; GCMS: m/z 305 [M^{+}]. Elemental Analysis (%) ($C_{13}H_{15}O_2N_5S$), Calculated; C 51.17, H 4.94, N 22.50, S 10.47. Found; C 51.10, H 4.85, N 22.24, S 10.94.

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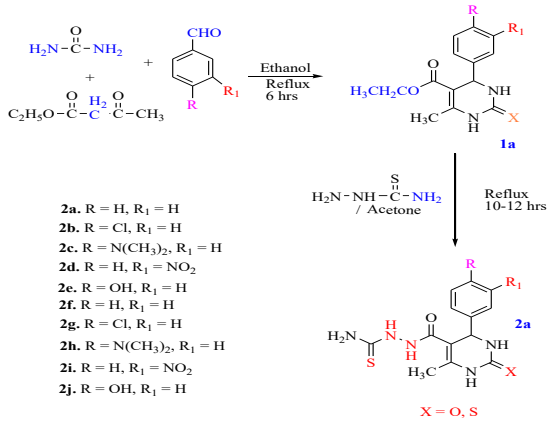
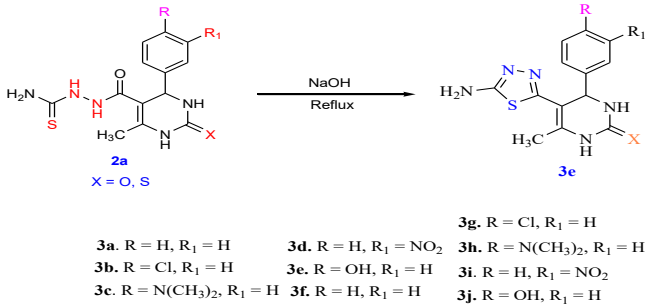


Scheme 1: Synthesis of hydrazine carbothioamide integrated pyrimidine **2a-j.**

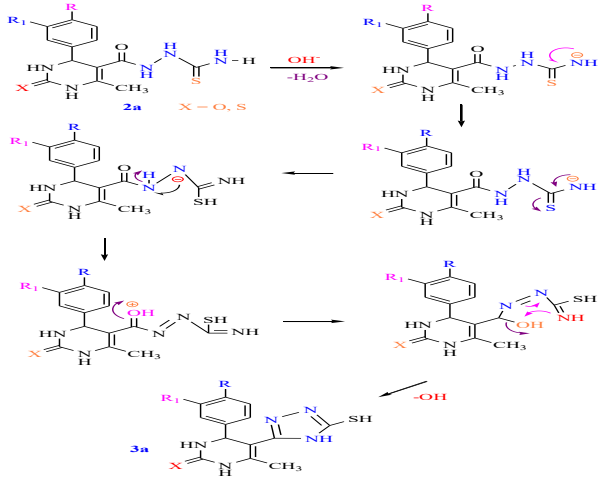
General procedure for Synthesis of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenylpyrimidin-2(1H)-one 3a. The synthesis of compounds (**3a-j**) **(Table 1)**, carbothioamide **2a** (3.05g, 0.01 mol) was added into (8g in 100ml) 8% NaOH it was heated, under refluxed for 4hrs. The reaction mixture was cooled to room temperature and acidified with dilute acetic acid then filtered and washed well with water and purified by recrystallization from alcohol as shiny crystals. m.p. 119-121^{0}C, yield 2.42g (85%). (Fig.1) ^{1}HNMR (400 MHz, DMSO-d_6) δ 2.304 (s, 3H), 3.217 (s, 1H), 5.507 (d, $^3J_{HH}$ = 3.6Hz, 1H), 6.975 (s, 1H), 7.268-7.338 (m, 5H), 7.766 (d, $^4J_{HH}$ = 2.4Hz, 1H), 9.217 (s, 1H). (Fig.2) ^{13}CNMR (400 MHz, DMSO-d_6) δ 17.74, 59.14, 99.24, 126.22, 127.21, 128.33, 144.84, 148.29, 152.15, 155.11, 165.32; (Fig.3) FT-IR (KBr) ŭ 3423 (NH), 3027 (Ar-H), 2968 (CH), 2235 (SH), 1654 (C=O), 1590 (C=N), 1373 (C-N), 1057 (N-N) cm^{-1}. GCMS: m/z 287 [M$^+$]. Elemental Analysis (%) ($C_{13}H_{13}ON_5S$), Calculated; C 54.38, H 4.56, N 24.39, S 11.13. Found; C 54.41, H 4.22, N 24.35, S 11.53.

RESULTS AND DISCUSSION

The synthesis of compounds (3a-j) followed **Scheme 1 and 2**, with compound 3a being the end product of reacting hydrazine carbothioamide compound 2a with refluxing NaOH. Pyrimidine ethyl ester 1 and thiosemicarbazide were reacted in acetone, and a condensation reaction was then performed to create hydrazine carbothioamide molecule 2a.



Scheme 2: Synthesis of triazole integrated pyrimidine compounds **3a-j.**



Scheme 3: Mechanism of triazole integrated pyrimidine compounds **3a-j.**

Benzaldehyde, ethylacetoacetate and urea or thiourea reacted in the presence of mineral acid and the Biginelli reaction was then performed to create the pyrimidine ethyl ester molecule 1a. IR (**Fig.3.**), ^{1}H-NMR (**Fig.1.**), ^{13}C-NMR(**Fig.2.**), GC-MS and CHN elemental analysis were used to confirm the structures of the synthesised compounds. The existence of C=O stretching peaks at 1724 cm^{-1} and N-H stretching peaks at 3365, 3241, and 3116 cm^{-1} in IR, as well as a singlet for the NH_2 group at 6.50 in the ^{1}H-NMR spectra, verified the production of compound 2a.

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Based on the C-N bond in the triazole ring, which resulted in an absorption band at 1373 cm^{-1} in its infrared spectrum, the structure of (3a) (**scheme 2**) was determined. The singlet at δ 3.21 in the ^{1}H-NMR spectrum was caused by SH functionality, spectral and analytical data were used to establish their structure (**Fig.1.**). The pyrimidine moiety's aromatic C-H stretching at 2968 cm^{-1} and 3027 cm^{-1}, the aliphatic C-H and N-N stretching band at 1053 cm^{-1} and the carbonyl absorption band at 1654 cm^{-1} of the NH-CO-NH group were all identified by IR and ^{1}H-NMR spectral data (3a) **Scheme 3**. The mass spectrum, which showed the molecular ion peak at m/z=287M^+, further confirmed the suggested structure.

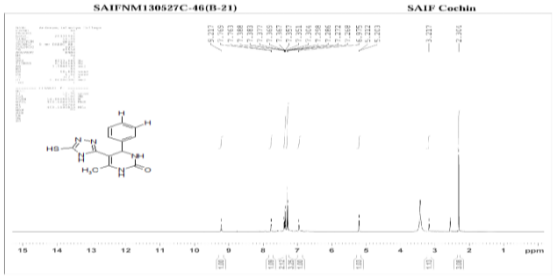
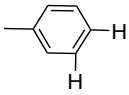
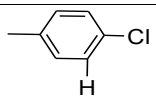
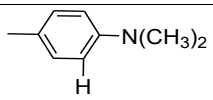
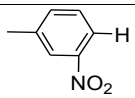
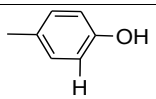
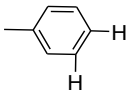
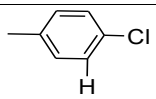
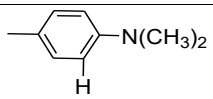
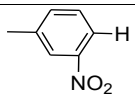
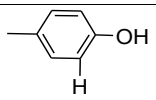


Fig.1. Triazole integrated pyrimidine derivatives ^{1}HNMR spectra for (3a)

Table 1: Triazole integrated pyrimidine compounds **3a-j.**

S.No.	R	X	M. Weight	M.P (^{0}C)	Yield (%)	Molecular Formula
3a		O	287	120	85	$C_{13}H_{13}ON_5S$
3b		O	321	115	88	$C_{13}H_{12}ON_5ClS$
3c		O	330	220	90	$C_{15}H_{18}ON_6S$
3d		O	332	118	84	$C_{13}H_{12}O_3N_6S$
3e		O	303	198	82	$C_{13}H_{13}O_2N_5S$
3f		S	303	123	74	$C_{13}H_{13}N_5S_2$
3g		S	337	175	78	$C_{13}H_{12}N_5ClS_2$
3h		S	346	155	82	$C_{15}H_{18}N_6S_2$
3i		S	348	115	76	$C_{13}H_{12}O_2N_6S_2$
3j		S	319	202	85	$C_{13}H_{13}ON_5S_2$

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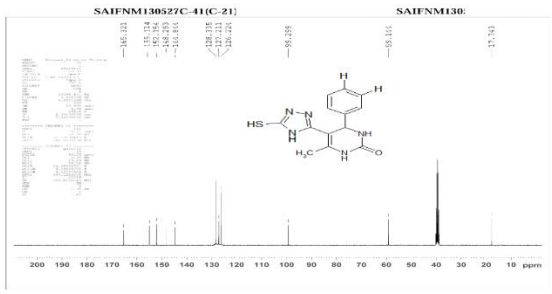

Fig.2. Triazole integrated pyrimidine derivatives - ^{13}CNMR for (3a)

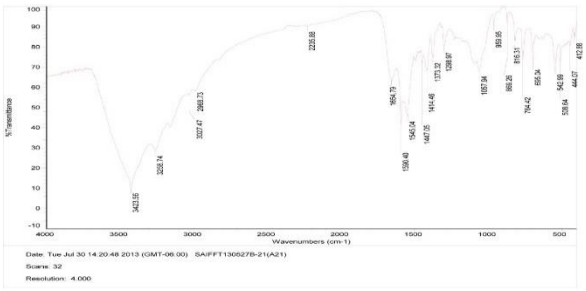

Fig.3. Triazole integrated pyrimidine derivatives- IR spectra for (3a)

Antifungal studies

Table 2 displays the results, which were obtained using amphotericin-B as a reference standard **Fig.4-6.** All of the investigated drugs demonstrated moderate to good inhibition against *Aspergillus Niger, Penicillium species,* and *Candida albicans* at 10 µg/mL concentrations, according to the analysis of antifungal screening results. Compounds 3a and 3g in particular have shown good activity and are extremely similar to the usual medication.

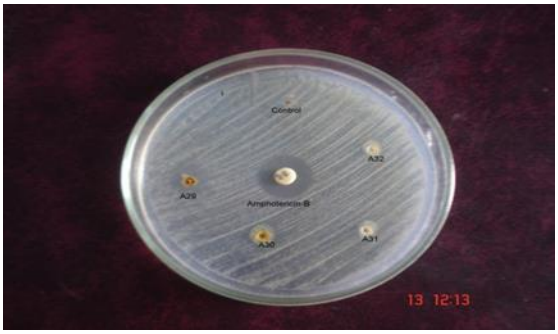

Fig.4. Candida albicans inhibition

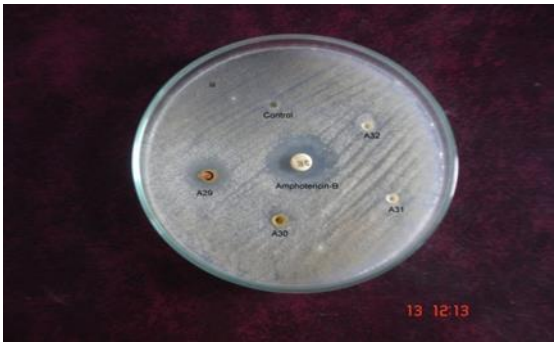

Fig.5. Penicillium species inhibition

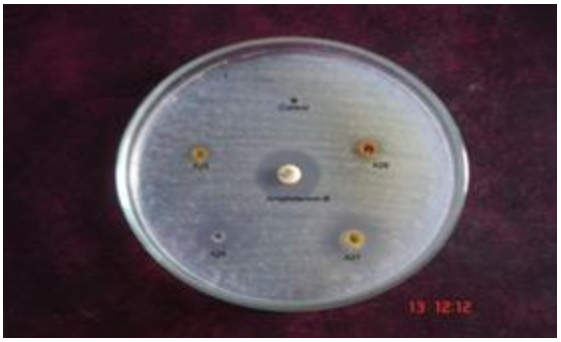

Fig.6. Aspergillus Niger inhibition

Table 2: Antifungal activities of compounds (3a-j) Std. *Amphotericin-B* **(15 mm)**

Compound	*Candida albicans* ***(mm)***	*Penicillium species* ***(mm)***	*Aspergillus niger* ***(mm)***
Control (DMSO)	0	0	0
3a	12	13	10
3b	10	10	6
3c	-	7	5
3d	-	-	5
3e	7	6	7
3f	9	8	8
3g	11	15	10
3h	8	10	6
3i	10	9	7

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3j	6	8	5
Concentration was 10 µg/mL@ 10% DMSO; "-" and "0" no inhibition zone.			

Graphical evaluation of Antifungal action

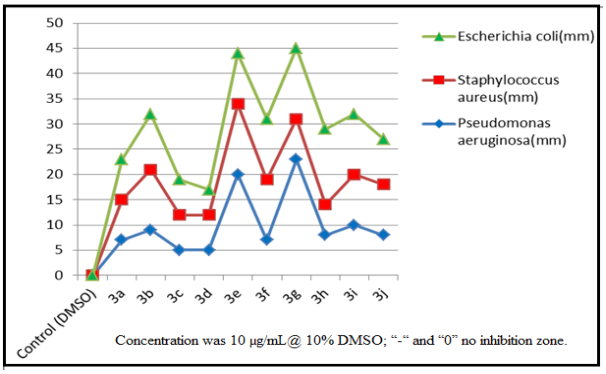

Fig.7. exploration of Antifungal action

CONCLUSIONS

At a concentration of 10 µg/mL, all of the 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl) compounds that were examined (3a–j) shown considerable inhibition. Certain drugs exhibit good inhibition and are comparable to the usual medication. The triazole heterocyclic compound's suppression of the three species of *Candida albicans, Penicillium species,* and *Aspergillus nigge*r is strengthened by the incorporation of pyrimidine rings and different substituted benzene rings. The comparison of antifungal action has showed in **Fig.7.** These compounds may have biological applications and research is ongoing to find safer, more affordable and more efficient alternatives.

AKNOWLEDGEMENT

The R&D departments of Priyadarshini Engineering College in Vaniyambadi, Tamilnadu, India and Dhaanish Ahmed Institute of Technology, K.G.Chavadi, Coimbatore-641105, Tamilnadu, India, provided support for this effort.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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