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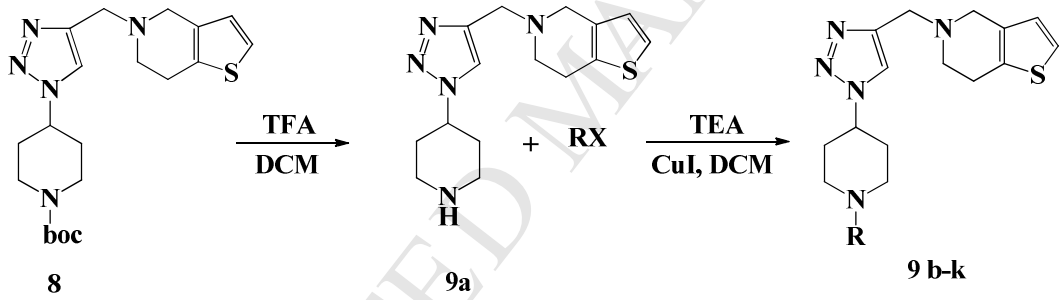
Graphical abstract

It is the first report for the novel amalgamation of 1,2,3 triazoles, piperidines, thieno pyridine rings and evaluation of their antifungal activity, revealing specificity towards fungal strains.



A novel amalgamation of 1,2,3-triazoles, piperidines and thieno pyridine rings and evaluation of their antifungal activity

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Abstract

It is the first report of the novel amalgamation of 1,2,3-triazoles, piperidines, thieno pyridine rings and evaluation of their antifungal activity. The synthesized compounds showed interesting moderate to good antifungal activity, wherein they were able to discriminate between the two species *A. flavus* and *A. niger* of the same genus. In addition, the main highlight of this series is the sensitivity of the fungal strain *C. neoformans* to the compounds having *p*-chloro benzoyl (**9h**), methane sulfonyl (**9i**) and *p*-methylbenzene sulfonyl (**9j**) attached to the piperazine nitrogen.

Keywords: 1,2,3-triazole, thieno pyridine, piperazine and antifungal activity.

1. Introduction

The eukaryotic microorganism fungi are vital opportunistic pathogens of humans which are developing drug resistant strains. In recent time several factors have contributed towards increasing life threatening systemic fungal infections, mainly due to development of drug resistant fungal strains. The development of drug resistance in fungal strains is commonly observed in severely ill and immune compromised patient population, including HIV-infected patients, patient recipients of transplant and patient suffering of cancer [1]. The other factors that have contributed to drug resistance are the frequently used more-invasive medical procedures and the treatment with broad-spectrum antibiotics. The majority of fungal infections are caused by *Candida* and *Aspergillus* species, with *Candida albicans* being the most common agent of fungal bloodstream infections. *Cryptococcus neoformans* has also become a major opportunistic fungal pathogen in patients receiving immunosuppressive treatment [1, 2].

The emergence of drug resistant fungi in the past decades has propelled the researchers around the globe to find new and efficacious drugs to solve

these problems by designing, synthesizing and biologically evaluating the developed molecules [3, 4]. Therefore, it is necessary to design new molecules which are not yet developed and to determine their biological activity. The literature survey revealed that till date the novel fusion of tetrahydrothieno pyridine [5, 6], 1,2,3-triazole[7, 8] and piperidine [9,10] has skipped through the vigilant eyes of the research groups. The main reason for the amalgamation of these rings was the diverse array of bioactivities possessed individually by them as mentioned below, and to study the effect of fusion of these rings on the biological activity of a molecule compromising these three rings on combined scale. The lack of efforts for the fusion of these three important cores into a single molecule and to study its biological activity propelled us to carry out this work.

The sulfur containing heterocycles have emerged as an important class of molecules in past decade due to their biodiversities from the industrial perspective and thus rise is seen in development of sulfur containing heterocycles. Tetrahydro thieno pyridine is one of such sulfur containing heterocycles having varied biological activities like anti-inflammatory, vasodilators and blood platelet aggregation inhibitory action [11]. The other nucleus, piperidine and its analogues are reported in literature for varied pharmacological activities like antibacterial [12], AChE inhibitors [13], antihistaminics [14] and antitubercular agents [15]. The piperidine and its derivatives are important building blocks in the synthesis of pharmaceuticals drug molecules like paroxetin, methylphenidate, raloxifene, minoxidil, risperidone and pethidine. The antifungal activity of the triazole analogues makes it a hot topic of research, especially in the industries. The research on 1,2,3-triazole and its derivatives like tazobactam enjoy a central position especially in medicinal chemistry attracting large number of researchers. The 1,2,3-triazoles analogues are also established as potent antineoplastic [16], antimicrobial [17], analgesic [18], anti-inflammatory [19], local anesthetic [20], anticonvulsant [21], antimalarial [22] and anti-HIV agents [23]. More recently there were reports of 1,2,3-triazole derivatives being used as DNA cleaving agents [24] and as a potential antitubercular agents [25].

2. Chemistry

In continuation of our work [26, 27], on the synthesis and biological evaluation of new heterocyclic molecules, we herein report the synthesis and antifungal evaluation of some novel structural scaffolds formed from fusion of 1,2,3-triazole, piperidine and tetrahydrothieno pyridine rings. The starting material *tert*-

butyl 4-azidopiperidine-1-carboxylate (**4**) was prepared according to our reported procedure in (**Scheme 1**) [26]. The reaction sequence for different title compounds is as outlined in (**Scheme 2** and **Scheme 3**). The compounds (**5**, **6**) were prepared as per the (**Scheme 2**). The *tert*-butyl 4-(4-((4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)methyl)-1*H*-1,2,3-triazol-1-yl) piperidine-1-carboxylate (**8**) was prepared by nucleophilic substitution reaction using *O*-mesyl derivative (**6**) and 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (THTP) (**7**) in acetonitrile at 60^{o}C for 6 hr. with 85 % yield (**Scheme 2**). The compound (**8**) was then subjected to deprotection to give 5-((1-(piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**9a**) by using trifluoroacetic acid (TFA) in dichloromethane with 87 % yield. The 5-((1-(piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-*c*] pyridine (**9a**) was subjected to substitution reaction in dichloromethane by using acyl chlorides/ alkyl chlorides to get the target derivatives (**9b-k**) in 82-91 % yield (**Table 1**, **Scheme 3**).

3. Pharmacology

3.1 Antifungal activity

All the synthesized compounds were screened for their *in-vitro* antifungal activity (**Table 2**). The antifungal activity was evaluated against different fungal strains including *Candida albicans* (NCIM3471), *Fusarium oxysporum* (NCIM1332), *Aspergillus flavus* (NCIM539), *Aspergillus niger* (NCIM1196) and *Cryptococcus neoformans* (NCIM576). Minimum inhibitory concentration (MIC, μg/mL) values of all compounds were determined using standard agar dilution method as per CLSI guidelines [28-31]. Miconazole was used as a standard drug for comparison of antifungal activity while dimethyl sulfoxide was used as solvent control.

4. Results and discussion

The antifungal data (**Table 2**) shows that all the tested compounds have moderate to good level of activity against all the tested fungal strain, except *C. neoformans*. The *C. neoformans* shows higher level of resistance to majority of synthesized compounds and in most cases this resistance was greater than 150 μg/mL. The compounds (**9i**) (MIC 25 to 50 μg/mL) and (**9h**) (MIC 40 to 45 μg/mL) are most active amongst the series, notably (**9i**) had promising activity (MIC of 25 μg/mL) against *C. neoformans*, but none of these compound is equivalent to miconazole. Among the synthesized series the compounds (**9b**, **9e**, **9j** and **9k**) were having the intermediate activity compared to standard, in which compound (**9j**) was found to be

most potent and specific against *A. niger* with lowest MIC value of 37.5 μg/mL. The remaining compounds (**9a**, **9c**, **9d**, **9f** and **9g**) were least active showing very low level of activity.

4.1 Structure activity relationship

The structure activity relationship reveals some very interesting facts about the strain specific variation in activity. Interestingly the synthesized compounds did not follow the same pattern in antifungal activity against different fungal strains and were able to discriminate the various targets in different strains. The highlights of structure activity relationship are,

1. **Specificity towards the *A. flavus***: The standard drug (Miconazole) showed the same degree of activity against *A. flavus* and *A. niger* which belongs to the same genus. But on the other hand the synthesized molecules (**9a-k**) irrespective of their side chains attached to the piperazine ring showed more specificity towards *A. flavus* compared to *A. niger.* It verified that the synthesized molecules (**9a-k**) were able to discriminate between the two species *A. flavus* and *A. niger* of the same genus.
2. **Effect of alkyl group**: The compound with unsubstituted piperazine nitrogen (**9a**) renders the molecule less active as compared to Miconazole but it showed activity against all the tested strains. The substitution of hydrogen (**9a**) on nitrogen of piperazine ring by methyl group (**9b**) increases the activity to intermediate level compared to compound (**9a**), but the compound was found to be inactive against *A. niger* and *C. neoformans.* The substitution of hydrogen (**9a**) on nitrogen of piperazine ring by ethyl group (**9c**) decreases the activity compared to (**9b**). But compound (**9c**) was found to be active against all the tested strains unlike that of (**9b**) and was especially more potent on *A. flavus.* It could be thus stated that as the chain length increase the molecule shows activity against all the tested strains and more specificity towards the particular strains.
3. **Effect of acyl group:** The effect of acyl substitution of hydrogen (**9a**) on nitrogen of piperazine ring was studied and it revealed some interesting results. The compound (**9d**) having an acetyl substitution gave intermediate active compound compared to miconazole for *C. albicans* and *F. oxysporum*, however it showed less activity for *A. Niger* and was fairly inactive for *A. flavus* and *C. neoformans*. The compound (**9e**) having an propionyl

substitution give intermediate active compound compared to standard, however unlike that of (**9d**) it was active against all the tested strains, which indicated that the increase in chain length plays an important role in antifungal activity. Lastly the compound (**9f**) having an isobutyryl substitution, resulted in less active compound compared to (**9d** and **9e**), but was moderately active against *A. flavus* and *A. niger*. This clearly highlights the crucial role of chain length and branching of acyl group in activity and strain specificity of compound. Thus for the antifungal activity the chain length must not be too short and preferably should avoid its branching.

4. **Effect of benzoyl group:** The benzoyl substituted compound (**9g**) lowers the activity and was fairly inactive for *F. oxysporum* and *A. niger*. The *p*-chlorobenzoyl compound (**9h**) gave one of the most active compounds of the series giving intermediate activity compared to the miconazole. The compound (**9h**) gave good activity compared to compound (**9g**) indicating the importance of the halogen substitution. The activity data suggest that the halogen analogues might help in improving the antifungal activity.
5. **Effect of sulfonyl group:** The methane sulfonyl substituted compound (**9i**) gave one of the most active compounds among the series. The introduction of the sulfonyl group enhanced the activity to great extent compared to (**9a**) but the same sulfonation does not work well with *p*-methylbenzene sulfonyl group (**9j**) when compared to (**9i**) except for *A. niger.* This could be attributed to the increase in length of the substituent [*p*-methylbenzene in case of compound (**9j**)]. Thus best antifungal activity could be achieved if the substituent used has a sulfonyl group.
6. **Effect of acyl and sulfonyl group:** The acyl substituents (**9d, 9e** and **9f**) gave improved activity compared with compound (**9a**). But the sulfonyl substituent (**9i** and **9j**) made the molecule most potent compounds amongst the series which could be attributed to the replacement of the carbonyl group by the sulfonyl group. In short substitution with sulfonyl group is better than acyl group for superior activity.
7. **Effect of benzyl and benzoyl group:** The introduction of benzyl group **(9k)** gave activity similar to the (**9a**) i.e. it neither improved nor decreased the activity of molecule compared to (**9a**). However the benzyl group was found

to have somewhat superior activity compared to that of the benzoyl group (**9g**).

8. **Equipotency against *C. neoformans*:** The main highlight of this series is the equipotency of compound (**9i**) and comparable activity by compounds (**9h**, **9j**) compare to miconazole against *C. neoformans.* While the rest of the synthesized molecules were almost inactive against the *C. neoformans.* In general it could be stated that the sulfonyl group is making the molecule more active against the fungal strain *C. neoformans*.

4.2 *Highlight of synthesis of 5-((1-(piperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivatives* (9a-k):

The remarkable highlight of synthesis of 5-((1-(piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine analogues is, (**i**) the first report for the synthesis of series of 5-((1-(piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine analogues; (**ii**) the first report of 5-((1-(piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-*c*] pyridine analogues, which has been synthesized and evaluated for antifungal activity; (**iii**) the main highlight of this series is the equipotency of compound (**9i**) against *C. neoformans*; (**iv**) the synthesized molecules (**9a-k**) were able to discriminate between the two species *A. flavus* and *A. niger* belonging to same genus; (**v**) to increase the antifungal activity the chain length must not be too short and preferably should avoid branching; (**vi**) to increase the antifungal activity the substitution could be having a sulfonyl group.

5. Conclusion

In conclusion, a novel amalgamation of 1,2,3-triazole, piperidine, tetrahydrothieno pyridine rings and evaluation of their antifungal activity has been carried out. The synthesized compounds showed interesting activity, wherein they were able to discriminate between the two species *A. flavus* and *A. niger* of the same genus. In addition the main highlight of this series is the selectivity and specificity for the fungal strain *C. neoformans* shown by the compounds (**9h**), (**9i**) and (**9j**).

6. Experimental protocols

6.1 Chemistry

The propargyl alcohol, copper iodide, triethyl amine, trifluoro acetic acid, substituted alkyl and acyl halides, tetrahydrothieno pyridine used were commercially available. Melting points were recorded on SRS Optimelt, melting point

apparatus and are uncorrected. IR spectra were taken on Bruker FT-IR 4000. ^{1}H NMR spectra were recorded on a 400 MHz Bruker spectrometer and ^{13}C NMR spectra were recorded on a 100 MHz Bruker spectrometer are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

6.1.1 ***Synthesis of tert-butyl 4-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate*** **(5):**

In a 50 mL round bottom flask, propargyl alcohol (10 mmol), triethyl amine (20 mmol) and compound (**4**) (10 mmol) was added in dimethyl formamide (5 ml), followed by CuI (2 mmol) and the resulting solution was stirred at room temperature for 10 hr. After completion of reaction (monitored by TLC, 20 % Ethyl acetate: *n*-hexane), solvent was removed in-vacuo and ethyl acetate (10 mL) was added to the residue and then extracted with 3 portions (3 x 10 mL) of distilled water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in-vacuo to get the desired compound (**5**), which was recrystallized using ethanol as solvent.

Pale Yellow Solid, Yield: 92 %, Melting Point: 173-175^{o}C

ES-MS *m/z* (%): 283 (M+H)

IR (KBr, cm^{-1}): 3400 (-OH), 3020 (C=CH), 2950 (C-CH), 1735 (C=O), 1640 (C=C), 1208 (C-N), 1100 (C-O-C).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.51 (s, 9H), 2.10-2.20 (m, *J* =7.0 Hz, 4H), 2.45-2.55 (m, *J* =7.0 Hz, 4H), 3.72 (m, 1H), 3.95 (s, 1H), 4.72 (d, *J* =2.0 Hz, 2H), 7.82 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 27.1, 29.4, 45.7, 55.7, 61.2, 82.3, 124.7, 144.1, 160.8.

6.1.2 ***Synthesis of tert-butyl 4-(4-(((methylsulfonyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate*** **(6):**

In a 50 mL round bottom flask, compound (**5**) (10 mmol) and triethyl amine (15 mmol) was added in 10 mL dichloromethane, stirred at room temperature for 5 minutes and then cooled to 0-5°C. Methane sulphonyl chloride (12 mmol) was added drop wise at 0-5°C, after addition the reaction mixture was allowed to attain room temperature and then stirred at room temperature for 2 hr. After completion of

reaction (monitored by TLC, 30 % Ethyl acetate: *n*-hexane), the reaction mixture was quenched by addition of distill water (10 mL). The organic layer was extracted with 3 portions (3 x 10 mL) of water and was washed with saturated $NaHCO_3$ (3 x 10 mL), the organic layer after extraction was separated, dried over anhydrous Na_2SO_4 and concentrated in-vacuo to afford compound (**6**), which was recrystallized using ethanol as solvent.

Off White Solid, Yield: 95 %, Melting Point: 210-212^oC

ES-MS *m/z* (%): 361 (M+H)

IR (KBr, cm^{-1}): 3025 (C=CH), 2910 (C-CH), 1730 (C=O), 1620 (C=C), 1238 (C-N), 1120 (C-O-C), 1030 (S=O).

^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.54 (s, 9H), 2.14-2.27 (m, *J* =7.0 Hz, 4H), 2.38-2.51 (m, *J* =7.0 Hz, 4H), 3.25 (s, 3H), 3.78 (m, *J* =7.0 Hz, 1H), 4.65 (d, *J* =7.0 Hz, 2H), 7.80 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 27.8, 29.7, 40.1, 45.3, 61.8, 65.1, 81.6, 123.9, 143.7, 160.1.

6.1.3 ***Synthesis of tert-butyl 4-(4-((4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl) methyl)-1H-1,2,3-triazol-1-yl) piperidine-1-carboxylate*** **(8):**

In a 50 mL round bottom flask, compound (**6**) (10 mmol), triethyl amine (20 mmol) and THTP **(7)** (10 mmol) was added in acetonitrile (10 mL) at room temperature. The resulting solution was then heated to 60°C for 6 hr. After completion of reaction (monitored by TLC, 30 % Ethyl acetate: *n*-hexane), the solvent was removed in-vacuo and ethyl acetate (10 mL) was added to the residue and then extracted with 3 portions (3 x 10 mL) of distilled water. The organic layers was dried over anhydrous Na_2SO_4 and concentrated in-vacuo to get the desired compound **(8)**, which was recrystallized using ethanol as solvent.

Pale Yellow Solid, Yield: 85 %, Melting Point: 214-216°C

ES-MS *m/z* (%): 404 (M+H)

IR (KBr, cm^{-1}): 3038 (C=CH), 2935 (C-CH), 1725 (C=O), 1628 (C=C), 1230 (C-N), 1125 (C-O-C).

^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.67 (s, 9H), 2.22-2.35 (m, *J* =7.0 Hz, 4H), 2.68-2.80 (m, *J* =7.0 Hz, 4H), 3.05-3.20 (m, *J* =7.4 Hz, 4H), 3.54 (d, *J* =7.4 Hz, 2H), 3.84 (m, *J* =7.4 Hz, 1H), 4.14 (s, 2H), 6.82 (d, *J* =9.5 Hz, 1H), 7.42 (s, 1H), 7.65 (d, *J* =9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.5, 25.8, 27.1, 28.3, 29.0, 29.7, 42.3, 46.2, 57.6, 59.2, 60.4, 61.3, 81.5, 114.5, 120.9, 124.1, 131.2, 133.6, 134.1, 161.3.

6.1.4 ***General procedure for synthesis of 5-((1-(piperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine*** **(9a):**

In a 50 mL round bottom flask, compound (**8**) (10 mmol) and trifluoro acetic acid (2 mmol) was added in dichloromethane (10 mL). The solution was stirred for 2 hr. at room temperature. After completion (monitored by TLC, 40 % Ethyl acetate: *n*-hexane), the mixture was extracted with saturated $NaHCO_3$ (3 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and on concentration in-vacuo gave the desired product (**9a**) in 87 % yield (**Table 1**, **entry 1**), which was recrystallized using ethanol as solvent.

6.1.5 ***General procedure for synthesis of 5-((1-(piperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivatives*** **(9b-k):**

In a 50 mL round bottom flask, compound (**9a**) (10 mmol), triethyl amine (20 mmol) and CuI (2 mmol) was added in dichloromethane (10 mL) and was stirred at room temperature for 5 minutes and then cooled to 0-5°C. To this cooled solution, different substituted alkyl or acyl halides (10 mmol) were added. The resulting solution was stirred for 2-3 hr. After completion (monitored by TLC, 40 % Ethyl acetate: *n*-hexane), was extracted with distilled water (3 x 10mL). The organic layer was dried over anhydrous Na_2SO_4 and on concentration in-vacuo gave the desired compounds (**9b-9k**) in 82-91 % yield (**Table 1**, **entry 2-11**), which were recrystallized using ethanol as solvent.

6.2 ***Spectral characterization***

6.2.1 ***5-((1-(piperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno [3,2-c]pyridine*** **(9a):**

Pale Yellow Solid, ES-MS *m/z* (%): 304 (M+H).

IR (KBr, cm^{-1}): 3300 (NH), 3045 (C=CH), 2890 (C-CH), 1660 (C=C), 1243 (C-N), 649 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.97 (s, 1H), 2.28-2.42 (m, *J* =7.0 Hz, 4H), 2.72-2.85 (m, *J* =7.0 Hz, 4H), 3.10-3.25 (m, *J* =7.0 Hz, 4H), 3.65 (s, 2H), 3.74 (m, *J* =7.0 Hz, 1H), 3.91 (s, 2H), 6.85 (d, *J* =9.5 Hz, 1H), 7.30 (d, *J* =9.5 Hz, 1H), 7.82 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 23.7, 27.1, 28.6, 42.4, 46.3, 54.7, 56.2, 60.1, 61.5, 122.9, 124.2, 125.5, 131.0, 133.9, 135.6.

6.2.2 *5-((1-(1-methylpiperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine* (9b):

Pale Yellow Solid, ES-MS *m/z* (%): 318 (M+H).

IR (KBr, cm^{-1}): 3060 (C=CH), 2900 (C-CH), 1671 (C=C), 1260 (C-N), 642 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.15 (s, 3H), 2.25-2.40 (m, *J* =7.0 Hz, 4H), 2.64-2.78 (m, *J* =7.0 Hz, 4H), 3.10-3.24 (m, *J* =7.4 Hz, 4H), 3.58 (s, 2H), 3.71 (m, *J* =7.4 Hz, 1H), 3.86 (s, 2H), 6.83 (d, *J* =9.5 Hz, 1H), 7.24 (d, *J* =9.5 Hz, 1H), 7.76 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 24.1, 27.4, 28.3, 47.1, 54.2, 55.8, 57.5, 58.6, 59.8, 61.7, 122.5, 124.5, 125.7, 131.4, 134.3, 135.8.

6.2.3 *5-((1-(1-ethylpiperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine* (9c):

Pale Yellow Solid, ES-MS *m/z* (%): 332 (M+H).

IR (KBr, cm^{-1}): 3052 (C=CH), 2914 (C-CH), 1645 (C=C), 1255 (C-N), 650 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.30 (s, 3H), 2.08-2.31 (m, *J* =7.0 Hz, 4H), 2.60-2.75 (m, *J* =7.0 Hz, 4H), 2.95 (q, *J* =7.4 Hz, 2H), 3.17-3.40 (m, *J* =7.4 Hz, 4H), 3.56 (s, 2H), 3.72 (m, *J* =7.4 Hz, 1H), 3.81 (s, 2H), 6.87 (d, *J* =9.5 Hz, 1H), 7.27 (d, *J* =9.5 Hz, 1H), 7.82 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.1, 23.7, 27.2, 28.0, 49.5, 53.7, 55.1, 56.2, 57.4, 58.6, 61.4, 122.7, 124.8, 126.2, 131.8, 134.5, 135.6.

6.2.4 *1-(4-(4-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-1H-1,2,3-triazol-1-yl)piperidin-1-yl)ethanone* (9d):

Pale Yellow Solid, ES-MS *m/z* (%): 346 (M+H).

IR (KBr, cm^{-1}): 3018 (C=CH), 2927 (C-H), 1715 (C=O), 1682 (C=C), 1270 (C-N), 649 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.05-2.26 (m, *J* =7.0 Hz, 4H), 2.40 (s, 3H), 3.25-3.40 (m, *J* =7.0 Hz, 4H), 3.45-3.60 (m, *J* =7.4 Hz, 4H), 3.65 (s, 2H), 3.75 (m, *J* =7.4 Hz, 1H), 3.86 (s, 2H), 6.80 (d, *J* =9.5 Hz, 1H), 7.32 (d, *J* =9.5 Hz, 1H), 7.74 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.8, 24.3, 27.5, 28.3, 42.1, 43.2, 55.4, 56.5, 57.4, 61.6, 122.9, 125.0, 126.5, 132.6, 134.1, 135.3, 175.4.

6.2.5 ***1-(4-(4-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-1H-1,2,3-triazol-1-yl)piperidin-1-yl)propan-1-one*** **(9e):**

Pale Yellow Solid, ES-MS *m/z* (%): 360 (M+H).

IR (KBr, cm^{-1}): 3035 (C=CH), 2944 (C-H), 1710 (C=O), 1650 (C=C), 1120 (C-N), 620 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.30 (s, 3H), 2.15-2.29 (m, *J* =7.0 Hz, 4H), 2.46 (q, *J* =7.4 Hz, 2H), 3.05-3.20 (m, *J* =7.0 Hz, 4H), 3.35-3.54 (m, *J* =7.4 Hz, 4H), 3.62 (s, 2H), 3.78 (m, 1H), 3.91 (s, 2H), 6.83 (d, *J* =9.5 Hz, 1H), 7.42 (d, *J* =9.5 Hz, 1H), 7.68 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.1, 24.0, 26.7, 27.6, 28.5, 42.6, 43.7, 55.1, 57.1, 58.2, 62.1, 123.1, 124.6, 125.7, 132.0, 133.5, 134.7, 175.9.

6.2.6 ***1-(4-(4-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-1H-1,2,3-triazol-1-yl)piperidin-1-yl)-2-methylpropan-1-one*** **(9f):**

Pale Yellow Solid, ES-MS *m/z* (%): 374 (M+H).

IR (KBr, cm^{-1}): 3032 (C=CH), 2942 (C-H), 1705 (C=O), 1680 (C=C), 1228 (C-N), 630 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.27 (s, 6H), 2.04-2.21 (m, *J* =7.0 Hz, 4H), 2.54 (m, *J* =7.0 Hz, 1H), 2.68-2.80 (m, *J* =7.4 Hz, 4H), 3.20-3.35 (m, *J* =7.0 Hz, 4H), 3.67 (s, 2H), 3.74 (s, 2H), 3.84 (m, *J* =7.0 Hz, 1H), 6.87 (d, *J* =9.5 Hz, 1H), 7.50 (s, 1H), 7.71 (d, *J* =9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.4, 24.3, 27.2, 27.9, 36.5, 43.1, 44.3, 55.2, 57.3, 58.5, 61.3, 123.3, 124.5, 125.8, 131.8, 133.7, 135.0, 172.5.

6.2.7 ***(4-(4-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-1H-1,2,3-triazol-1-yl) piperidin-1- yl) (phenyl)methanone*** **(9g):**

Pale Yellow Solid, ES-MS *m/z* (%): 408 (M+H).

IR (KBr, cm^{-1}): 3020 (C=CH), 2925 (C-H), 1712 (C=O), 1667 (C=C), 1250 (C-N), 642 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.12 -2.28 (m, *J* =7.0 Hz, 4H), 2.72-2.85 (m, *J* =7.0 Hz, 4H), 3.24-3.40 (m, *J* =7.4 Hz, 4H), 3.60 (s, 2H), 3.72 (s, 2H), 3.87 (m, *J* =7.4 Hz, 1H), 6.81 (d, *J* =9.5 Hz, 1H), 7.42-7.58 (m, *J* =7.0 Hz, 5H), 7.68 (s, 1H), 7.78 (d, *J* =9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 24.3, 27.0, 28.1, 43.2, 44.0, 55.5, 57.3, 58.4, 61.0, 123.1, 124.2, 125.4, 126.2, 127.0, 128.4, 130.4, 132.5, 134.2, 135.6, 174.7.

6.2.8 ***(4-chlorophenyl)(4-(4-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-1H-1,2,3-triazol-1-yl)piperidin-1-yl)methanone*** **(9h):**

Pale Yellow Solid, ES-MS *m/z* (%): 443 (M+H).

IR (KBr, cm^{-1}): 3055(C=CH), 2962 (C-H), 1684 (C=O), 1654 (C=C), 1262 (C-N), 639 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.15-2.30 (m, *J* =7.0 Hz, 4H), 2.65-2.80 (m, *J* =7.0 Hz, 4H), 3.34-3.48 (m, *J* =7.4 Hz, 4H), 3.63 (s, 2H), 3.77 (s, 2H), 3.87 (m, *J* =7.4 Hz, 1H), 6.78 (d, *J* =9.5 Hz, 1H), 7.22-7.40 (m, *J* =7.0 Hz, 4H), 7.65 (s, 1H), 7.80 (d, *J* =9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 24.5, 27.4, 28.1, 43.0, 43.8, 55.2, 56.3, 57.1, 61.0, 123.2, 124.0, 125.1, 128.1, 129.4, 130.4, 131.2, 132.6, 134.3, 135.4, 171.2.

6.2.9 ***5-((1-(1-(methylsulfonyl)piperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine*** **(9i):**

Pale Yellow Solid, ES-MS *m/z* (%): 382 (M+H).

IR (KBr, cm^{-1}): 3012 (C=CH), 2937 (C-H), 1642 (C=C), 1230 (C-N), 1042 (S=O), 648 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.98 (s, 3H), 2.14-2.32 (m, *J* =7.0 Hz, 4H), 2.65-2.77 (m, *J* =7.0 Hz, 4H), 3.05-3.20 (m, *J* =7.4 Hz, 4H), 3.50 (s, 2H), 3.75 (m, *J* =7.4 Hz, 1H), 4.05 (s, 2H), 6.90 (d, *J* =9.5 Hz, 1H), 7.46 (s, 1H), 7.72 (d, *J* =9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 23.1, 26.0, 27.3, 40.3, 45.7, 46.2, 56.4, 57.2, 58.0, 61.5, 121.7, 123.6, 126.4, 131.2, 133.6, 134.1.

6.2.10 ***5-((1-(1-tosylpiperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c] pyridine*** **(9j):**

Pale Yellow Solid, ES-MS *m/z* (%): 458 (M+H).

IR (KBr, cm^{-1}): 3025 (C=CH), 2917 (C-H), 1635 (C=C), 1248 (C-N), 1035 (S=O), 641 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.97 (s, 3H), 2.12 -2.30 (m, *J* =7.0 Hz, 4H), 2.55-2.70 (m, *J* =7.0 Hz, 4H), 3.05-3.20 (m, *J* =7.4 Hz, 4H), 3.47 (s, 2H), 3.71 (m, *J* =7.4 Hz, 1H), 4.12 (s, 2H), 6.87 (d, *J* =9.5 Hz, 1H), 7.34 (s, 1H), 7.49-7.60 (m, *J* =7.0 Hz, 4H), 7.65 (d, *J* =9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.7, 23.4, 25.6, 26.3, 43.9, 44.7, 56.1, 57.4, 58.3, 60.7, 122.9, 123.8, 126.1, 127.0, 128.6, 129.8, 131.2, 133.6, 134.5, 138.2, 145.2.

6.2.11 ***5-((1-(1-benzylpiperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine*** **(9k):**

Pale Yellow Solid, ES-MS *m/z* (%): 394 (M+H).

IR (KBr, cm^{-1}): 3018 (C=CH), 2925 (C-H), 1626 (C=C), 1272 (C-N), 639 (C-S).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.08-2.21 (m, *J* =7.0 Hz, 4H), 2.51-2.65 (m, *J* =7.0 Hz, 4H), 3.05-3.22 (m, *J* =7.4 Hz, 4H), 3.44 (s, 2H), 3.61 (s, 2H), 3.75 (m, *J* =7.4 Hz, 1H), 4.12 (s, 2H), 6.81 (d, *J* =9.5 Hz, 1H), 7.37 (s, 1H), 7.50-7.65 (m, *J* =7.0 Hz, 5H), 7.71 (d, *J* =9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.7, 27.3, 28.5, 51.2, 52.1, 54.3, 57.6, 58.7, 60.3, 64.8, 122.7, 124.1, 125.0, 126.7, 127.6, 128.5, 129.4, 130.5, 131.2, 133.4, 135.1, 138.2.

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Table 1. Synthesis of 5-((1-(piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine derivatives (9a-k).[a,b]

Compound	Substituent (-R)	Time (min)	Yield[c] (%)	Melting point (°C)
9a	*Hydrogen*	60	87	185-187
9b	*Methyl*	120	89	178-180
9c	*Ethyl*	100	85	184-186
9d	*Acetyl*	80	87	156-158
9e	*Propionyl*	150	86	191-193
9f	*Isobutyryl*	100	89	179-181
9g	*Benzoyl*	100	90	164-166
9h	*p- chlorobenzoyl*	150	84	170-172
9i	*Methane sulfonyl*	60	91	189-191
9j	*p-methylbenzene sulfonyl*	60	85	192-194
9k	*Benzyl*	180	82	174-176

a. Reaction condition (**9a**): Compound **(8)** (10 mmol), TFA (2 mmol) in (10 mL) of dichloromethane at room temperature.

b. Reaction condition (**9b-k**): Compound **(9a)** (10 mmol), alkyl or acyl halides (10 mmol) in 10 mL of dichloromethane, triethyl amine (20 mmol) and CuI (2 mmol) at 0-5°C.

c. Isolated yields.

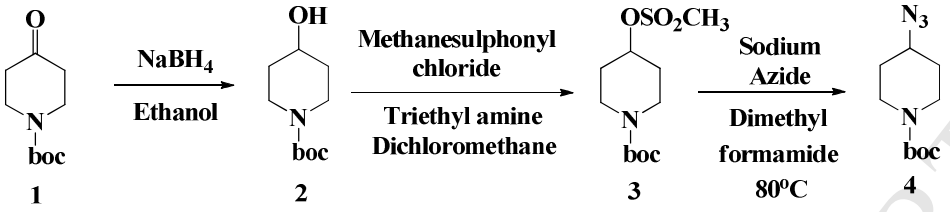
Table 2. Antifungal activity of the synthesized compounds (9a-k).

Compound	MIC Values (µg/mL)[a]				
	C. albicans	***F. oxysporum***	***A. flavus***	***A. niger***	***C. neoformans***
9a	50	90	60	100	100
9b	40	70	40	*	*
9c	90	100	35	47.5	150
9d	40	45	*	100	*
9e	50	60	30	*	*
9f	100	100	35	47.5	150
9g	90	*	65	*	100
9h	45	40	40	42.5	45
9i	50	30	40	40	25
9j	60	70	45	37.5	40
9k	50	75	60	100	90
Miconazole	**25**	**25**	**12.5**	**12.5**	**25**

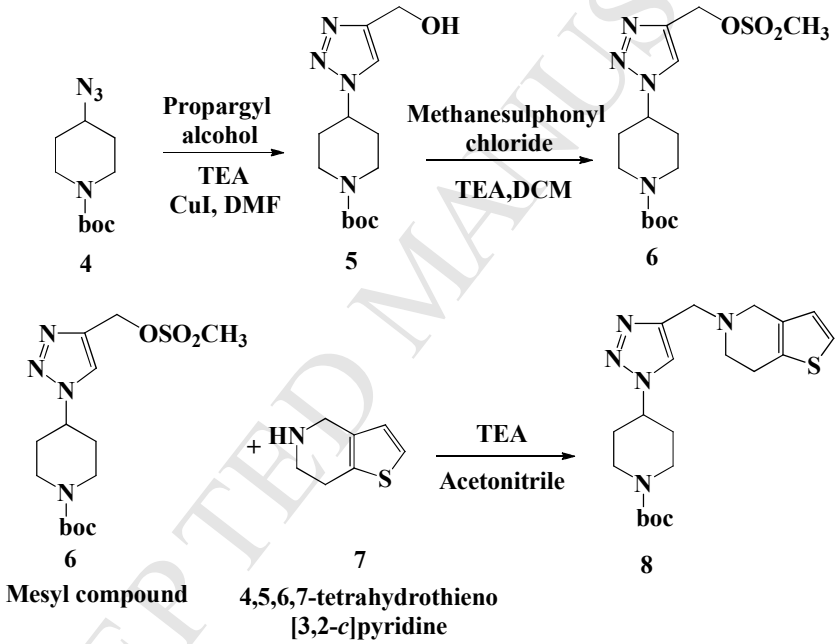
* - Activity not reported up to 200 µg/mL.

[a] - Values are average of three readings.

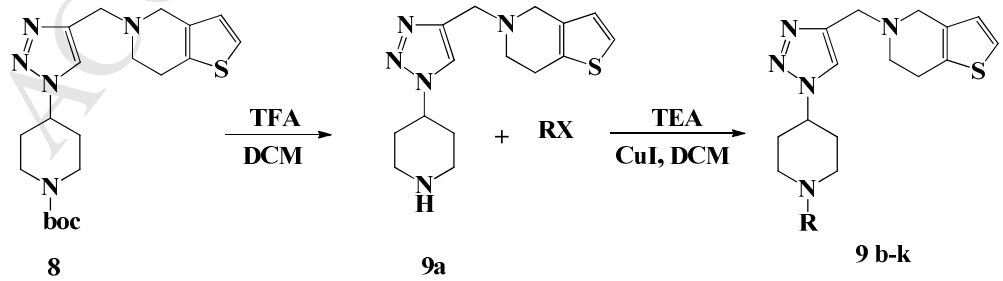
Scheme 1. Synthesis of *tert*-butyl 4-azidopiperidine-1-carboxylate [20].



Scheme 2. Synthesis of *tert*-butyl 4-(4-(((methylsulfonyl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)piperidine-1-carboxylate.



Scheme 3. Synthesis of 5-((1-(piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine derivatives.



A novel amalgamation of 1,2,3 triazoles, piperidines and thieno pyridine rings and evaluation of their antifungal activity

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***Highlight of synthesis of 5-((1-(piperidin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivatives* (9a-k):**

The remarkable highlight of synthesis of 5-((1-(piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine analogues is,

(i) Successful novel amalgamation of piperidine, triazole and thienopyridine;

(ii) Evaluation of antifungal activity which revealed interesting data;

(iii) Specificity of compounds towards fungal strains;

(iv) Role of chain length and sulphonyl group.