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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, and antimicrobial evaluation of novel naphthalene-based 1,2,4-triazoles

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Abstract In order to search for new bioactive molecules with significant antimicrobial action, a series of 1,2,4-triazole and naphthalene analogs bearing structurally diverse substituents, *N*-(3-mercapto-5-(naphthalen-1-yl)-4*H*-1,2,4-triazol-4-yl)(aryl)amides **3a–l** were synthesized in good yield by a multi-step synthetic procedure. Their antimicrobial activity was screened against various Gram-positive and Gram-negative bacteria and fungi. Compounds **3a**, **3f**, **3g**, **3j**, and **3k** exerted strong inhibition of the investigated bacterial and fungal strains compared to control antibiotic ampicillin and antifungal griseofulvin. On the basis of statistical analysis, it is observed that the compounds give significant co-relation. All the synthesized compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data.

Keywords 1,2,4-Triazole · Naphthalene · Antibacterial activity · Antifungal activity · MIC

Introduction

In the last few decades, though significant progress has been made in treatment and control strategies of microbial infections by introducing new diagnostic, monitoring tools and combination therapy, it still continues to be a severe problem. Thus, we embarked in our programme which is aimed at development of novel drug molecules with improved potential for treatment of microbial infections and with decreased probability of developing drug resistance. Heterocyclic compounds are commonly used as scaffolds on which pharmacophores are arranged to provide potent and selective drugs (Krchnak and Holladay, 2002; Nefzi *et al.*, 1997; Terrett *et al.*, 1995). This is especially true for five-membered ring heterocyclic compounds, which serve as core components of a large number of substances that possess a wide range of interesting biological activities (Desai *et al.*, 2010a, b, 2011a, b).

1,2,4-Triazole is a versatile lead molecule for developing potential bioactive agents. Derivatives of this particular lead structure containing ring systems have been incorporated to yield a wide variety of therapeutically interesting activities including antibacterial (Holla *et al.*, 1994), anti-inflammatory (Sahin *et al.*, 2001), CNS depressant (Parmar *et al.*, 1972), anti-tubercular (Dabak *et al.*, 2003), anti-HIV (Alvarez *et al.*, 1994), and anti-proliferative (Manfredini *et al.*, 2000). 1,2,4-Triazole system is a structural element of many drugs that have anti-mycotic activity such as fluconazole, intraconazole, and voriconazole (Haber, 2001). Also, there are other known drugs containing 1,2,4-triazole group, e.g., triazolam, rizatriptan, nefazodone, vorozole, ribavirin, letrozole, uniconazole, alprazolam, and etizolam. Anastrozole is an aromatase inhibitor, which interrupts synthesis of estrogen in the body (Wellington and Faulds 2002). 1-Acyl-1*H*-[1,2,4]triazole-3,5-diamine analogs are found to be potent as anticancer and cyclin-dependent kinase inhibitors (Lin *et al.*, 2005). Literature described triazole as an antiplatelet agent (Cunha *et al.*, 2003), selective GSK-3 inhibitor (Olesen *et al.*, 2003), dopamine D_2-receptor ligand related to schizophrenia (Menegatti *et al.*, 2003), ghrelin receptor (Demange *et al.*, 2007), anticonvulsant (Kelley *et al.*, 1995), selective adenosine A_{2A} receptor antagonist (Peng *et al.*, 2004),

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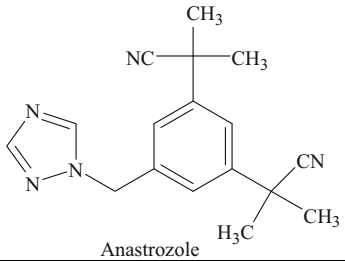
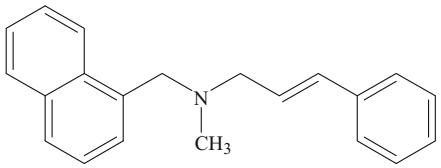
β-lactamase inhibitor (Micetich *et al.*, 1987), inhibitor of hormone sensitive lipase (Ebdrup *et al.*, 2004), and $GABA_A$ receptor agonist (Russell *et al.*, 2005).

Naphthalene derivatives have been identified as a new range of potent antimicrobial, effective against wide range of human pathogens. Substituted naphthalene showed a variety of biological activities such as antihypotensive (Tandon *et al.*, 2004), enhanced affinity for human 5-HT_{1DB} (h5-HT_{1B}) serotonin-receptor (Ismaiel *et al.*, 1997), antagonists of human CCR8 (Jenkins *et al.*, 2007), antitumor, DNA photocleaving (Li *et al.*, 2005), antimalarial (Harpstrite *et al.*, 2008), non-nucleoside HIV-1 reverse transcriptase inhibitor (Zhan *et al.*, 2009), cytotoxicity, and anti-tubulin (Medarde *et al.*, 2004). Several naphthalene containing drugs are available, such as nafacillin, naftifine, tolnaftate, terbinafine, etc. Naftifine is an antifungal drug for the topical treatment of tinea pedis, tinea cruris and tinea corporis (fungal infections) (Wilson, 2004). The synthesis of new compounds is of vital importance due to increasing drug resistance. Moreover, it is important to obtain therapeutically active compounds having less toxic effects.



Anastrozole



Naftifine

Motivated by the aforementioned findings and in continuation of our ongoing research program in the field of 1,2,4-triazole and naphthalene derivatives as antimicrobial agents, we have developed an efficient procedure for the synthesis of a new class of heterocyclic molecules in which both moieties are present. The structures of synthesized compounds are assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. These compounds are evaluated for their antimicrobial screening on different strains of bacteria and fungi.

Results and discussion

Chemistry

The synthetic strategies adopted to obtain the target compounds are shown in Scheme 1. Present scaffold **3** is a part of synthesis of new chemical entities in the form of antimicrobial agents. Scaffold **2** is prepared in an excellent yield by reacting 1-naphthohydrazide **(1)** with carbon disulfide and potassium hydroxide. Compound **2** on cyclization with *N*-aminoarylcarboxamides afforded *N*-(3-mercapto-5-(naphthalen-1-yl)-4*H*-1,2,4-triazol-4-yl)arylamides **(3a–l)**.

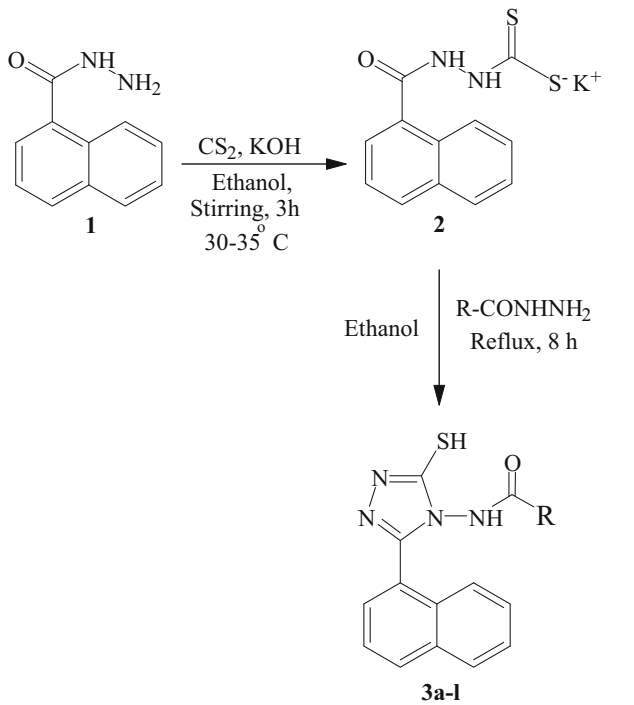
Characterization

Characterization of the newly synthesized compounds of this series was accomplished by IR, NMR, mass spectra, and elemental analysis.

IR spectrum of title compound **3g** (molecular formula $C_{19}H_{13}ClN_4OS$, m.w. 380.85 gm/mol) has given stretching vibration at 3328 cm^{-1} over the range, showing medium intensity absorption peak corresponding to secondary amine in amide linkage. Absorption bands at 3079 and 3052 cm^{-1} over the ranges are due to Ar–H stretching vibrations. Weak intensity absorption band at 2565 cm^{-1} is due to stretching vibration of S–H. Strong intensity absorption band at 1716 cm^{-1} is due to stretching vibration of C=O of amide linkage, while the weak intensity absorption band at 1618 cm^{-1} corresponds to a C=N stretching vibration and medium intensity absorption band is observed due to C=C stretching vibration at 1552 and 1445 cm^{-1}. Strong intensity absorption band at 789 cm^{-1} is attributed to the stretching vibration of C–Cl bond.

In ^{1}H NMR spectra, it has been observed from the chemical structure of compound **3g** that pair of carbons, e.g., C-8 and C-9 are attached to chemically equivalent protons, which appeared as doublet at a $\delta = 7.39$ ppm. The SH protons on C-12 appeared as a singlet at $\delta = 3.38$ ppm due to the influence of attachment with triazole ring. Protons attached to carbons C-1, C-2, C-3, C-7, and C-10 in naphthalene ring appeared as a multiplet at $\delta = 7.19$–7.63 ppm, respectively. Proton of the secondary amine appeared as a singlet at $\delta = 9.87$ ppm. Protons attached to C-15, C-16, C-17, and C-19 of chlorophenyl ring appeared as a multiplet at $\delta = 7.16$–7.91 ppm, respectively.

Looking at ^{13}C NMR, chemical shifts of the final compound **3g** vary from $\delta = 164.4$–124.6 ppm. Carbon nucleus under the influence of a strong electronegative environment appeared downfield, e.g., C-13, i.e., carbonyl



Scheme 1 Synthetic route of the final compounds **(3a–l)**

carbon, which is present in amide linkage directly linked to nitrogen, has a chemical shift value of $\delta = 164.4$ ppm. Carbons present in triazole nucleus C-11 and C-12 on both sides are directly attached to nitrogen atom. So, carbon C-11 gave a chemical shift at $\delta = 147.1$ ppm and C-12 gave a chemical shift at $\delta = 151.6$ ppm. Carbon C-12 was more downfield than C-11 due to direct attachment to thiol group. Carbon C-18 appeared at $\delta = 134.6$ ppm due to the influence of chloro group. Carbons are present in naphthalene ring C-1, C-2, C-3, C-4, C-5, and C-6 gave a chemical shift between $\delta = 124.6$–134.9 ppm, respectively. Carbons of the phenyl ring C-8 and C-9 which are equivalent carbons gave a chemical shift at $\delta = 126.00$ ppm, while carbons C-7 and C-10 which are also equivalent gave a chemical shift at $\delta = 127.5$ ppm.

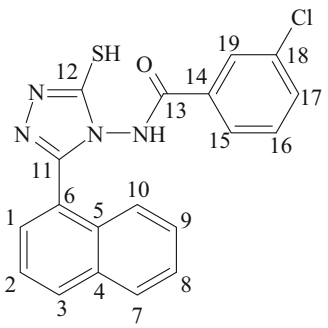


Fig. 1 Carbon enumeration of the final compound-**3g**

Carbons of chloro phenyl ring C-14, C-15, C-16, C-17, and C-19 gave a chemical shift between $\delta = 126.2$–133.2 ppm, respectively. Carbon enumeration of compound **3g** is described in Fig. 1.

Antimicrobial screening

Many of the newly synthesized compounds are found to exhibit good to excellent antimicrobial activity. From antimicrobial activity data (Table 1), it is observed that compounds **3a** (–C_6H_5), **3f** (2-Cl–C_6H_4), **3 g** (3-Cl–C_6H_4), **3j** (4-NO_2–C_6H_4), and **3k** (8-NO_2–$C_{10}H_7$) are most active. For antibacterial activity, compounds **3b** (2-CH_3–C_6H_4), **3c** (2-OCH_3–C_6H_4), **3h** (3-NO_2–C_6H_4), and **3l** (–$C_{10}H_7$–OCH_2) possess good activity against *E. coli*, while compounds **3f** and **3j** possess very good activity against *E. coli*. Compound **3f** contains chloro substitution at 2-position and compound **3j** contains 4-nitro substitution. Replacement of hydrogen by 3-chloro substituent in **3a** leads to **3g**, enhances the activity against *E. coli*. Compounds **3b** (2-CH_3–C_6H_4), **3f** (2-Cl–C_6H_4), **3h** (3-NO_2–C_6H_4), **3i** (4-OH–C_6H_4), and **3k** (8-NO_2–$C_{10}H_7$) possess good activity against *P. aeruginosa*. When there is no substitution on phenyl ring in **3a** it possesses very good activity, while replacement with 4-nitro group in compound **3j**, enhances the activity against *P. aeruginosa*. Compounds **3c** (2-OCH_3–C_6H_4), **3d** (C_6H_5–CH_2), **3g** (3-Cl–C_6H_4), **3j** (4-NO_2–C_6H_4), **3k** (8-NO_2–$C_{10}H_7$), and **3l** ($C_{10}H_7$–OCH_2) possess good activity against *S. aureus*, while compounds **3 h** (3-NO_2–C_6H_4) and **3i** (4-OH–C_6H_4) possess very good activity against *S. aureus*. Compounds **3b** and **3g** possess good activity against *S. pyogenes*, compound **3b** contains methyl group and compound **3g** contains chloro group as substitution. For antifungal activity, compounds **3b** (2-CH_3–C_6H_4), **3c** (2-OCH_3–C_6H_4), **3e** (2-OH–C_6H_4), **3h** (3-NO_2–C_6H_4), **3i** (4-OH–C_6H_4), and **3l** (–$C_{10}H_7$–OCH_2) displayed good activity against *C. albicans*. When we replace the substitution with 8-NO_2–$C_{10}H_7$ in compound **3k**, it showed very good activity against *C. albicans*. Furthermore, replacement with chloro group at 2 and 3-position, i.e., **3f** and **3g**, respectively, and nitro group at 4-position in **3j**, the activity is enhanced and it shows excellent activity against *C. albicans*. Compounds **3f** (2-Cl–C_6H_4) and **3k** (8-NO_2–$C_{10}H_7$) possess good activity against *A. niger*, at the same time if we replace it by groups like 3-chloro and 4-nitro in **3g** and **3j**, it possesses very good activity against *A. niger*. Compounds **3b** (2-CH_3–C_6H_4) and **3h** (3-NO_2–C_6H_4) possess good activity against *A. clavatus*. It is our observation that replacement of chloro group at third position in **3g**, nitro group at fourth position in **3j** and nitro group at eighth position in **3k** raises activity and it possesses excellent activity against *A. clavatus*. The enhancement of activity of these compounds is due to the

Table 1 Results of antibacterial and antifungal screening of compounds **3a–l**

S. no.	–R	Minimum inhibitory concentration (MIC) in μg/ml ± SD				Minimum inhibitory concentration (MIC) in μg/ml ± SD		
		E. coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
3a	$-C_6H_5$	500 ± 4.93	50 ± 2.64***	500 ± 3.78*	1000 ± 2.64*	1000 ± 3.78**	1000 ± 3.05	1000 ± 3.21
3b	$-2-CH_3-C_6H_4$	100 ± 3.05	100 ± 3.46*	500 ± 3.21	100 ± 4.04**	200 ± 3.05***	500 ± 3.51	100 ± 4.05*
3c	$-2-OCH_3-C_6H_4$	100 ± 3.78***	250 ± 3.21*	250 ± 2.08***	500 ± 2.51	200 ± 3*	200 ± 4.50***	500 ± 4.35
3d	$-C_6H_5-CH_2$	500 ± 4.50	500 ± 3.51	250 ± 2.08	200 ± 2.64*	1000 ± 4.50	500 ± 4.21	500 ± 4.16**
3e	$-2-OH-C_6H_4$	1000 ± 1*	1000 ± 1**	500 ± 4.04	500 ± 2.51*	500 ± 3.21	500 ± 2.08	200 ± 3.78***
3f	$-2-Cl-C_6H_4$	50 ± 1***	100 ± 3.60**	500 ± 3.78**	500 ± 3.78	50 ± 1***	100 ± 3.05*	250 ± 3.78
3g	$-3-Cl-C_6H_4$	25 ± 1***	250 ± 4.72	250 ± 3.05*	100 ± 3.51***	50 ± 2.05**	50 ± 2.64**	50 ± 3.51*
3h	$-3-NO_2-C_6H_4$	100 ± 2.64	100 ± 3.05	100 ± 4.16	500 ± 3.78	200 ± 4.04	200 ± 4	100 ± 3.05**
3i	$-4-OH-C_6H_4$	250 ± 4.58	100 ± 2.08*	100 ± 4.04**	500 ± 4.50	500 ± 4.93	500 ± 3.78	500 ± 4.58
3j	$-4-NO_2-C_6H_4$	50 ± 4.05	25 ± 1**	250 ± 4.50	500 ± 3.05	50 ± 3.21*	50 ± 3.05***	50 ± 3.21***
3k	$-8-NO_2-C_{10}H_7$	200 ± 3.21***	100 ± 3**	250 ± 2.64	250 ± 2.08*	100 ± 2.30**	100 ± 3.05*	50 ± 2.46*
3l	$-C_{10}H_7-OCH_2$	100 ± 3.05**	250 ± 3.78	250 ± 3.21*	500 ± 3.51**	500 ± 2.51*	500 ± 2.64	500 ± 4**
	Ampicillin	100 ± 2.05	100 ± 1.0	250 ± 1.52	100 ± 2.06	–	–	–
	Griseofulvin					500 ± 0.58	100 ± 1	100 ± 1.15

±*SD* standard deviation, *** $P < 0.001$ extremely significant , ** $P < 0.01$ moderately significant, * $P < 0.05$ significant

All values are presented as mean of 10 experiments ($n = 6$). All significant differences are considered from control value 0.00

presence of chloro and nitro groups in title compounds. We have discussed and compared antibacterial and antifungal activities based on standard drugs ampicillin and griseofulvin, respectively.

Antibacterial assay

The newly synthesized compounds are screened for their antibacterial activity against Gram positive bacteria (*Staphylococcus aureus* (MTCC-96), *Streptococcus pyogenes* (MTCC-442)), and Gram-negative (*Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688)). Antibacterial activity is carried out by serial broth dilution method (Desai *et al.*, 2010a, b, 2011a, b; Al-Bayati and Al-Mola, 2008). Standard strains which are used for antimicrobial activity are procured by The Institute of Microbial Technology, Chandigarh. Compounds **(3a–l)** are screened for their antibacterial activity in six sets against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus pyogenes* at different concentrations of 1000, 500, 200, 100, 50, and 25 μg/ml as shown in Table 1. The compounds found to be active in primary screening are similarly diluted to obtain 100, 50, and 25 μg/ml concentrations. Ten microgram per milliliter suspensions are further inoculated on appropriate media and growth is noted after 24 and 48 h. The lowest concentration, which shows no growth after spot subculture is considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as MIC. The test mixture should contain 10^8 cells/ml. Standard drug used in this study is 'ampicillin' for evaluating antibacterial activity which shows 100, 100, 250, and 100 μg/ml MIC against *E. coli, P. aeruginosa, S. aureus*, and *S. pyogenes*, respectively. For bacterial growth, in the present protocol, we have used Muller Hinton broth at 37°C in aerobic condition for 24–48 h.

Antifungal assay

The same compounds are tested for antifungal activity in six sets against *Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus* at various concentrations of 1000, 500, 200, and 100 μg/ml as shown in Table 1. Results are recorded in the form of primary and secondary screening. Synthesized compounds are diluted to 1000 μg/ml concentration, as a stock solution. Synthesized compounds which are found to be active in this primary screening are further tested in second set of dilution against all microorganisms. The lowest concentration, which shows no growth after spot subculture is considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as MIC. Test mixture should contain 10^8 spores/ml MIC. Griseofulvin is used as a standard drug for antifungal activity, which shows 500, 200, 100 and 50 μg/ml MIC against *C. albicans*, *A. niger*, and *A. clavatus*, respectively. Results of antimicrobial evaluation of derivatives **(3a–l)** are shown in Table 1. For fungal growth, in the present protocol, we have used Sabourauds dextrose broth at 22°C in aerobic condition for 72 h.

Statistical analysis

Standard deviation value is expressed in terms of ±SD. On the basis of calculated value by using One-way ANOVA method followed by independent two sample *t* test, it has been observed that differences below 0.001 level are considered statistically significant. Compounds **(3a–l)** are screened for their antibacterial and antifungal activities in six sets (*n*) against bacteria and fungi used in the present protocol.

Materials and methods

Completion of reaction and purity of all compounds is checked on aluminum coated TLC plates 60 F_{245} (E. Merck) using *n*-hexane: ethyl acetate (7.5:2.5 V/V) as mobile phase and visualized under ultraviolet (UV) light or iodine vapor. Melting points are determined on an electro thermal melting point apparatus and are reported uncorrected. Elemental analysis (% C, H, N) is carried out by a Perkin-Elmer 2400 CHN analyser. IR spectra of all compounds have been recorded on a Perkin-Elmer FT-IR spectrophotometer in KBr. ^{1}H NMR and ^{13}C NMR spectra are recorded on Bruker (400 MHz) spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Mass spectra are obtained on Schimadzu LCMS 2010 spectrophotometer. Anhydrous reactions are carried out in dried glassware in nitrogen atmosphere. In the conventional method, compounds are synthesized by using Random synthesizer. Buchi Rotavapor is used for distillation.

Experimental

*Preparation of 1-naphthohydrazide **(1)***

Compound 1-naphthohydrazide **(1)** is prepared according to literature method (Mathew *et al.* 2006).

*Preparation of potassium 2-(2-naphthoyl)hydrazinecarbodithioate **(2)***

To a solution of KOH in alcohol (99.9%) (0.1 mol), 1-naphthohydrazide **1** (0.1 mol) and carbon disulfide (0.1 mol) are added drop wise with constant stirring and the mixture is stirred for 3 h. Resulting white solid is separated out, filtered, and washed with petroleum ether.

*General procedure for preparation of 3-mercapto-5-(naphthalene-1-yl)-N-aryl-4H-1,2,4-triazole-4-carboxamides **(3a–l)***

A mixture of compound **2** (0.1 mol) and *N*-amino-aryl-carboxamides (0.1 mol) in ethanol (95%) (25 ml) containing is refluxed for 6 h. The solution is poured into cold water and subsequent is acidified to pH 8 with hydrochloric acid resulting in white precipitates. The solid product is filtered, washed with water, and recrystallized from alcohol (99.9%).

*N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)benzamide **(3a)***

Yield: 78%; m.p.: 156–158°C; IR (KBr, cm^{-1}): 3335 (–NH stretching, secondary amine), 3085, 3057 (C–H stretching, aromatic ring), 2575 (–SH stretching, thiol), 1715 (C=O stretching, amide), 1610, 1535, 1455 (C=N, C=C, aromatic ring stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.30 (s, 1H, –SH), 7.10–7.70 (m, 12H, Ar–H), 9.85 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 124.4, 126.1, 126.5, 127.2, 127.6, 128.1, 128.5, 132.8, 133.7, 133.1, 134.7, 137.3, 147.1, 151.6, 164.3; LCMS (*m/z*): 348 (M^+). Anal. Calcd. For $C_{19}H_{14}N_4OS$ C-65.87, H-4.07, N-16.17; Found: C-65.74, H-4.02, N-16.21%.

*N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)-2-methylbenzamide **(3b)***

Yield: 74%; m.p.: 215–217°C; IR (KBr, cm^{-1}): 3331 (–NH stretching, secondary amine), 3087, 3054 (C–H stretching,

aromatic ring), 2918 (C–H stretching, $–CH_3$), 2570 (–SH stretching, thiol), 1711 (C=O stretching, amide), 1618, 1542, 1448 (C=N, C=C, aromatic ring stretching), 1391 (C–H bending, $–CH_3$); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.21 (s, 3H, $–CH_3$), 3.32 (s, 1H, –SH), 7.15–7.79 (m, 11H, Ar–H), 9.84 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 17.2, 124.2, 126, 126.2, 127.3, 128.2, 128.5, 130.5, 132.5, 132.6, 134.5, 134.6, 137.1, 137.5, 147.3, 151.6, 164.1; LCMS (*m/z*): 360 (M^+). Anal. Calcd. For $C_{20}H_{16}N_4OS$: C-66.65, H-4.47, N-15.54; Found: C-66.70, H-4.52, N-15.60%.

N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)-2-methoxybenzamide ***(3c)***

Yield: 73%; m.p.: 199–201°C; IR (KBr, cm^{-1}): 3338 (–NH stretching, secondary amine), 3082, 3062 (C–H stretching, aromatic ring), 2943 (C–H stretching, $–OCH_3$), 2565 (–SH stretching, thiol), 1713 (C=O stretching, amide), 1610, 1544, 1452 (C=N, C=C, aromatic ring stretching), 1400 (C–H bending, $–OCH_3$), 1207 (C–O–C stretching, $–OCH_3$); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.30 (s, 1H, –SH), 3.46 (s, 3H, $–OCH_3$), 7.17–7.82 (m, 11H, Ar–H), 9.85 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 55.8, 117.9, 119.4, 120.8, 124.7, 126.4, 126.6, 127.5, 128.2, 128.6, 132.4, 133.4, 134.7, 137.1, 147.2, 151.6, 157.4, 164.3; LCMS (*m/z*): 376 (M^+). Anal. Calcd. For $C_{20}H_{16}N_4O_2S$: C-63.81, H-4.28, N-14.88; Found: C-63.72, H-4.36, N-14.77.

N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)-2-phenylacetamide ***(3d)***

Yield: 77%; m.p.: 186–188°C; IR (KBr, cm^{-1}): 3329 (–NH stretching, secondary amine), 3079, 3067 (C–H stretching, aromatic ring), 2869 (C–H stretching, $–CH_2–$), 2568 (–SH stretching, thiol), 1712 (C=O stretching, amide), 1618, 1541, 1435 (C=N, C=C, aromatic ring stretching), 1456 (C–H bending, $–CH_2–$); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.30 (s, 1H, –SH), 3.90 (s, 2H, $–CH_2$) 7.12–7.68 (m, 11H, Ar–H), 9.81 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 37.8, 124.6, 126.1, 126.4, 127.2, 127.9, 128.5, 129.3, 129.5, 132.7, 134.7, 135.6, 137.3, 147.2, 151.4, 166.4; LCMS (*m/z*): 360 (M^+). Anal. Calcd. For $C_{20}H_{16}N_4OS$: C-66.65, H-4.47, N-15.54; Found: C-66.53, H-4.58, N-15.62%.

2-Hydroxy-N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)benzamide ***(3e)***

Yield: 70%; m.p.: 225–227°C; IR (KBr, cm^{-1}): 3410 (O–H stretching, –OH), 3334 (–NH stretching, secondary amine), 3071, 3047 (C–H stretching, aromatic ring), 2562 (–SH stretching, thiol), 1710 (C=O stretching, amide), 1620, 1540, 1451 (C=N, C=C, aromatic ring stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.34 (s, 1H, -SH), 7.16–7.87 (m, 11H, Ar–H), 9.78 (s, 1H, –OH), 9.86 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 117.5, 120.1, 121.2, 124.3, 126.2, 126.5, 127.2, 128.1, 128.6, 132.6, 133.8, 134.7, 137.3, 147.5, 151.3, 155.1, 164.4; LCMS (*m/z*): 362 (M^+). Anal. Calcd. For $C_{19}H_{14}N_4O_2S$: C-62.97, H-3.89, N-15.46; Found: C-62.85, H-3.77, N-15.58%.

2-Chloro-N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)benzamide ***(3f)***

Yield: 74%; m.p.: 175–177°C; IR (KBr, cm^{-1}): 3329 (–NH stretching, secondary amine), 3075, 3041 (C–H stretching, aromatic ring), 2571 (–SH stretching, thiol), 1712 (C=O stretching, amide), 1612, 1547, 1440 (C=N, C=C, aromatic ring stretching), 780 (C–Cl stretching, C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.36 (s, 1H, –SH), 7.17–7.89 (m, 11H, Ar–H), 9.87 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 124.2, 126.1, 126.3, 126.6, 127.5, 128.2, 129.2, 130.2, 132.1, 132.5, 134.5, 134.6, 134.4, 137.3, 147.2, 151.4, 164.5; LCMS (*m/z*): 380 (M^+). Anal. Calcd. For $C_{19}H_{13}ClN_4OS$: C-59.92, H-3.44, N-14.71; Found: C-59.85, H-3.52, N-14.63%.

3-Chloro-N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)benzamide ***(3g)***

Yield: 71%; m.p.: 186–188°C; IR (KBr, cm^{-1}): 3328 (–NH stretching, secondary amine), 3079, 3052 (C–H stretching, aromatic ring), 2565 (–SH stretching, thiol), 1716 (C=O stretching, amide), 1618, 1552, 1445 (C=N, C=C, aromatic ring stretching), 789 (C–Cl stretching, C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.38 (s, 1H, –SH), 7.16–7.91 (m, 11H, Ar–H), 9.87 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 124.6, 125.2, 126, 126.2, 127.3, 127.5, 128.3, 130.1, 132.8, 133.2, 134.3, 134.7, 137.1, 134.9, 147.1, 151.6, 164.4; LCMS (*m/z*): 380 (M^+). Anal. Calcd. For $C_{19}H_{13}ClN_4OS$: C-59.92, H-3.44, N-14.71; Found: C-59.85, H-3.52, N-14.75%.

N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)-3-nitrobenzamide ***(3h)***

Yield: 69%; m.p.: 195–197°C; IR (KBr, cm^{-1}): 3334 (–NH stretching, secondary amine), 3083, 3052 (C–H stretching, aromatic ring), 2567 (–SH stretching, thiol), 1712 (C=O stretching, amide), 1605, 1557, 1440 (C=C, C=N, aromatic ring stretching), 1485 (NO_2 group, asymmetric stretching), 1355 (NO_2 group, symmetric stretching); ^{1}H NMR

(400 MHz, DMSO-d_6, δ, ppm): 3.37 (s, 1H, –SH), 7.19–8.15 (m, 11H, Ar–H), 9.89 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 123.3, 124.1, 126.4, 126.6, 127.2, 127.4, 128.1, 129.4, 132.5, 133.6, 134.7, 135.1, 137.4, 147.2, 147.4, 151.2, 164.5; LCMS (*m/z*): 391 (M^+). Anal. Calcd. For $C_{19}H_{13}N_5O_3S$: C-58.30, H-3.35, N-17.89; Found: C-58.22, H-3.42, N-17.91%.

4-Hydroxy-N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)benzamide ***(3i)***

Yield: 76%; m.p.: 211–213°C; IR (KBr, cm^{-1}): 3405 (O–H stretching, –OH), 3340 (–NH stretching, secondary amine), 3078, 3039 (C–H stretching, aromatic ring), 1716 (C=O stretching, amide), 1613, 1551, 1442 (C=N, C=C, aromatic ring stretching), 2567 (–SH stretching, thiol); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.36 (s, 1H, –SH), 7.16–7.89 (m, 11H, Ar–H), 9.78 (s, 1H, –OH), 9.86 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 116.1, 124.5, 126.3, 126.5, 126.7, 127.1, 128.5, 128.9, 132.6, 134.7, 137.4, 147.3, 151.3, 160.9, 164.3; LCMS (*m/z*): 362 (M^+). Anal. Calcd. For $C_{19}H_{14}N_4O_2S$: C-62.97, H-3.89, N-15.46; Found: C-62.85, H-3.77, N-15.58%.

N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)-4-nitrobenzamide ***(3j)***

Yield: 73%; m.p.: 169–171°C; IR (KBr, cm^{-1}): 3340 (–NH stretching, secondary amine), 3082, 3043 (C–H stretching, aromatic ring), 2571 (–SH stretching, thiol), 1717 (C=O stretching, amide), 1617, 1542, 1450 (C=N, C=C, aromatic ring stretching), 1472 (NO_2 group, asymmetric stretching), 1350 (NO_2 group, symmetric stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.38 (s, 1H, –SH), 7.18–8.18 (m, 11H, Ar–H), 9.88 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 124, 124.4, 126.2, 126.5, 127.5, 128.4, 129.5, 132.7, 134.6, 137.5, 138.9, 147.4, 151.5, 152.1, 164.5; LCMS (*m/z*): 391 (M^+). Anal. Calcd. For $C_{19}H_{13}N_5O_3S$: C-58.30, H-3.35, N-17.89; Found: C-58.42, H-3.32, N-17.94%.

N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)-8-nitro-2-naphthamide ***(3k)***

Yield: 69%; m.p.: 205–207°C; IR (KBr, cm^{-1}): 3332 (–NH stretching, secondary amine), 3080, 3038 (C–H stretching, aromatic ring), 2874 (C–H stretching, –CH_2–), 2570 (–SH stretching, thiol), 1718 (C=O stretching, amide), 1611, 1551, 1444 (C=N, C=C, aromatic ring stretching), 1470 (NO_2 group, asymmetric stretching), 1452 (C–H bending, –CH_2–), 1354 (NO_2 group, symmetric stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.34 (s, 1H, –SH), 7.16-8.10 (m, 13H, Ar–H), 9.83 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 37.9, 123.1, 124.3, 126.3, 126.5, 127.1, 128.5, 128.7, 128.9, 132.4, 134.6, 137.3, 142.8, 145.6, 147.5, 151.6, 166.7; LCMS (*m/z*): 441 (M^+). Anal. Calcd. For $C_{23}H_{15}N_5O_3S$: C-62.58, H-3.42, N-15.86; Found: C-62.52, H-3.38, N-15.79%.

N-(3-mercapto-5-(naphthalen-1-yl)-4H-1,2,4-triazol-4-yl)-2-(naphthalen-2-yloxy)acetamide ***(3l)***

Yield: 75%; m.p.: 187–189°C; IR (KBr, cm^{-1}): 3328 (–NH stretching, secondary amine), 3078, 3047 (C–H stretching, aromatic ring), 2890 (C–H stretching, –CH_2–), 2564 (–SH stretching, thiol), 1714 (C=O stretching, amide linkage), 1602, 1548, 1440 (C=N, C=C, aromatic ring stretching), 1459 (C–H bending, –CH_2–), 1120 (C–O–C stretching, ether linkage); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.30 (s, 1H, –SH), 5.10 (s, 2H, –CH_2), 6.67–7.78 (m, 14H, Ar–H), 9.85 (s, 1H, –CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 62.7, 113.4, 118.3, 124.5, 124.8, 126.3, 126.4, 126.5, 126.7, 127.5, 127.8, 128.3, 132.6, 133.6, 133.8, 134.7, 137.2, 147.3, 151.7, 156.2, 167.6; LCMS (*m/z*): 426 (M^+). Anal. Calcd. For $C_{24}H_{18}N_4O_2S$: C-67.59, H-4.25, N-13.14; Found: C-67.64, H-4.32, N-13.21%.

Conclusion

In the present investigation, we have synthesized 1,2,4-triazole and naphthalene containing derivatives as micro-organism growth inhibitors. The antibacterial screening data reveal that among the synthesized compounds screened, **3a**, **3f**, **3g**, **3h**, **3i**, and **3j** showed significant bacterial growth inhibition almost greater than that of the standard drugs. As far as antifungal screening results are concerned **3f**, **3g**, **3j**, and **3k** displayed significant activity. Hence, it is concluded that there is an ample scope for further study in developing these as good lead compounds, which can be used in the bigger scenario such as drug design or development of antimicrobial therapeutics.

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