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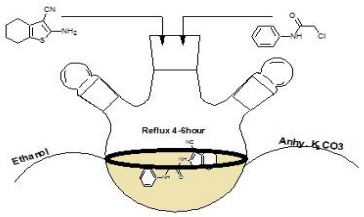
Synthesis and Anti-microbial Screening of *N*-(3-cyano-4,5,6,7-tetrahydro-1 benzothiophen-2-yl)-2-(arylphenyl)acetamide

Maharshi B Shukla[1], Jyotindra B Mahyavanshi[2*], Prakash J Joshi[3], Bharat Patel[3]

[1]Dr. Indu-Dayal Meshri College of Science and Technology, Patan, Gujarat, India
[2]Department of Chemistry, Sankalchand Patel University, Gujarat, India
[3]Sheth M. N. Science College, Patan, Gujarat, India

ABSTRACT

Reactions of 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile with 2-chloro-N-(aryl)-acetamides gave N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-(arylphenyl)acetamide. The novel compounds structure has been established on the basis of their substituted N-chloro aryl acetamide derivatives. All the compounds were characterized by FT-IR, Mass, [1]H-NMR spectroscopy. These new compounds were evaluated for their in vitro antibacterial activity and anti-fungal activity.



Keywords: 2-Amino-4,5,6,7-tetrahydro-1-benzothiopheane-3-carbonitrile, Acetamide, Anti-fungal activity, Bacterial activity

INTRODUCTION

The rapidly expanding population of immune compromised patient results in a corresponding increase of diseases caused by bacteria, fungi and other yeast. Infection caused by these microorganisms pose a serious challenge to the medical community and highlight the importance and urgent need for new, more potent and selective non-traditional antimicrobial agent. The incidence of bacterial infections has increased dramatically in recent years [1]. The widespread use of antibacterial and antifungal drugs and their resistance against bacterial and fungal infections has led to serious health hazards. The resistance of wide spectrum antibacterial agents has prompted discovery and modification towards new antifungal and antibacterial drugs [2,3].

In continuation of our interest on chemistry of functionalized chloroacetamide derivatives [4]. Because of the high mobility of chlorine atom and reactive N-H group, compounds containing chloroacetamide moiety are known to be useful synthetic scaffolds for design of aziridines [5] lactams [6], piperazines [7], oxazolidines [8], imidazolidines and tetrahydropyrimidines–precursors of heterocyclic carbenes [9], macrocyclic ligands [10], dendrimers [11]. 2-Chloracetamide derivatives found application in solid-state chemistry [12], in synthesis of aminoacids [13], natural compounds [14] and their homologs [15], pharmacologically promising substances [16] and biomarkers [17] reagents for polymer modification [18], ion-exchange resins for heavy and radioactive metal sorption [19]. Chloroacetamide pesticides [20] and dye [21] are also well known. Thus, investigation of 2-chloroacetamide chemistry is an actual task both from theoretical and applied viewpoints.

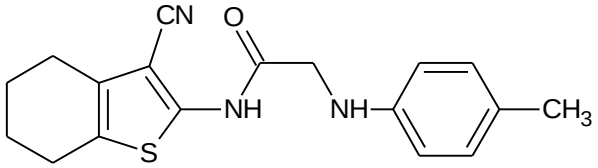
The exploration of new heterocycles that can accommodate potency to multiple biological targets remains an intriguing scientific endeavor. In continuation to extend our research [22] it was sought of interest to 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile derivatives hoping to go a step forward in the field of antimicrobial agents and thus, we undertook design, synthesis and examination of anti-microbial activities of novel *N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-(arylphenyl)acetamide as anti-microbial precursors. 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile nucleus is a fertile source of bioactivity in the area of drug discovery because of its varied biological activities viz. antimicrobial [23,24], anti-inflammatory [25-27], antituberculosis [28,29] and anticonvulsant [30] anticancer [31,32].

MATERIAL AND METHODS

All the melting points were recorded on Centex melting point apparatus and are uncorrected. IR spectra in KBr were recorded on Schimadzu FTIR spectrophotometer in cm^{-1}. ^{1}H-NMR spectra were recorded in Deuterated Chloroform ($CDCl_3$) or Dimethyl Sulfoxide (DMSO) on a Bruker DRX-400 MHZ NMR instrument. Chemical shifts were reported in ppm using TMS as internal standard on (δ) scale. Completion of the reactions was monitored time to time by Thin Layer Chromatography (TLC) using E-Merck 0.25 mm silica gel plates and toluene: acetone (8:2) as solvent system.

RESULTS AND DISCUSSION

Reaction between 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile(1) with 2-chloro-N-(aryl)-acetamides(2) give compounds *N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2 (arylphenyl)acetamide were obtained in 60-81% yield. Mass spectral data support the proposed structures. The mass spectrum showed various characteristic peaks. A peak at *m/z*=326 (m+1) was assigned to the molecular ion.



The FTIR spectrum showed absorption bands at, 3423 cm^{-1} (-NH- stretching in amine), 3296 cm^{-1} (-NH- stretching in amide), 1654 cm^{-1} (C=O stretching in amide), 1588 cm^{-1}(S-C=O stretching in thioether linkage), 2229 cm^{-1} and (C≡N) 2918 cm^{-1} (-CH_2-) in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring respectively.

The ^{1}H-NMR spectrums of showed characteristic signals at 4.11 ppm which was assigned to the methylene protons. Signals at 9.22 ppm which was assigned to the amide proton. A multiplet at 1.64-1.67 ppm and A multiplet at 2.53-2.56 ppm were assigned to the 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. A dd 7.14 ppm and dd 7.56 ppm were assigned to the 4-methyl phenyl ring. Signals at 9.92 ppm which was assigned to the amine proton

General procedure of synthesis

Step–I: Synthesis of 2-chloro-N-(aryl)-acetamides 2(a-j)

In benzene (30.0 ml), chloroacetylchloride (0.02 mol) and 4-6 drops of triethyl amine was added, the mixture was stirred in ice bath. The solution of aryl amine (0.02 mol) in benzene (30.0 ml) was added drop-wise and refluxed for 4 h and the reaction mixture was cooled to ambient temp. The resulting ppt. were filtered and washed with benzene purified by re-crystallization from alcohol.

Step–II: *N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-(arylphenyl)acetamide 3(a-j)

A mixture of 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (0.01 mol), 2-chloro-N-(aryl)-acetamides (0.01 mol) in 30 ml ethanol and anhydrous K_2CO_3 (0.02 mol) was refluxe for 4-6 h at room temperature and poured into ice. The product was filtered and washed with cold water. Recrystallized from alcohol. The progress of reaction was monitored by TLC using Toluene: Acetone (8:2) as Eluent. Purifications of all the synthesized compounds were achieved by recrystallization and purity of each compound was monitored by TLC.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(4-methylphenyl)amino]acetamido (3a)**

FTIR (KBr, cm^{-1}): 3423 cm^{-1} (-NH-) 3296 cm^{-1} (-NH- in amide), 1654 cm^{-1} (in C=O amide), 1588 cm^{-1} (S-C=O in thioether), 754 cm^{-1} (C-S) 2229 cm^{-1} (CN), 2918 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.11(s, 2H, CH_2), 9.22(s, 1H, -NH-), 9.92 (s, 1H, -NH-), 1.64-1.67 (m, 4H, Ar-H) 2.53-2.56 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.14 (dd, J=8, 2H, Ar-H), 7.56 (dd, 2H, J=8, Ar-H) at 4-methyl phenyl ring. Anal. Calcd. For $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.38; H, 5.84; N, 12.85. Yield: 72%. m.p. 136-139°C, Mass(M+)-325.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(4-fluorophenyl)amino]acetamido (3b)**

FTIR (KBr, cm^{-1}): 3457 cm^{-1} (-NH-) 3316 cm^{-1} (-NH- in amide), 1647 cm^{-1} (in C=O amide), 1594 cm^{-1} (S-C=O in thioether), 769 cm^{-1} (C-S) 2233 cm^{-1} (CN), 2904 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.31 (s, 2H, CH_2), 9.29 (s, 1H, -NH-), 9.85 (s, 1H, -NH-), 1.70-1.73 (m, 4H, Ar-H) 2.47-2.50 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.23 (dd, J=8, 2H, Ar-H), 7.7.48 (dd, 2H, J=8, Ar-H) at 4-fluoro phenyl ring. Anal. Calcd. For $C_{17}H_{16}FN_3OS$: C, 61.99; H, 4.90; N, 12.76. Found: C, 66.87; H, 4.83; N, 12.79. Yield: 68%. m.p. 175-178°C, Mass(M+)-329.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(3-chloro4- fluorophenyl)amino]acetamide (3c)**

FTIR (KBr, cm^{-1}): 3488 cm^{-1} (-NH-) 3323 cm^{-1} (-NH- in amide), 1641 cm^{-1} (in C=O amide), 1579 cm^{-1} (S-C=O in thioether), 782 cm^{-1} (C-S) 2217 cm^{-1} (CN), 2926 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.20 (s, 2H, CH_2), 9.19 (s, 1H, -NH-), 9.94 (s, 1H, -NH-), 1.72-1.75 (m, 4H, Ar-H) 2.49-2.52 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.22-7.74 (m, 3H, Ar-H), at 3-chloro-4-fluoro phenyl ring. Anal. Calcd. For $C_{17}H_{15}ClFN_3OS$: C, 56.12; H, 4.16; N, 11.55. Found: C, 56.04; H, 4.09; N, 11.47. Yield: 66%. m.p. 153-156°C, Mass(M+)-363.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(4-chlorophenyl)amino]acetamide(3d)**

FTIR (KBr, cm^{-1}): 3439 cm^{-1} (-NH-) 3276 cm^{-1} (-NH- in amide), 1647 cm^{-1} (in C=O amide), 1599 cm^{-1} (S-C=O in thioether), 759 cm^{-1} (C-S) 2216 cm^{-1} (CN), 2911 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.38 (s, 2H, CH_2), 9.22 (s, 1H, -NH-), 9.85 (s, 1H, -NH-), 1.75-1.78 (m, 4H, Ar-H) 2.58-2.61 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.18 (dd, J=8, 2H, Ar-H), 7.68 (dd, 2H, J=8, Ar-H) at 4-chloro phenyl ring. Anal. Calcd. For $C_{17}H_{16}ClN_3OS$: C, 59.04; H, 4.66; N, 12.15. Found: C, 58.97; H, 4.57; N, 12.10. Yield: 71%. m.p. 124-127°C, Mass(M+)-345.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(4-methoxyphenyl)amino]acetamide(3e)**

FTIR (KBr, cm^{-1}): 3432 cm^{-1} (-NH-) 3291 cm^{-1} (-NH- in amide), 1641 cm^{-1} (in C=O amide), 1584 cm^{-1} (S-C=O in thioether), 754 cm^{-1} (C-S) 2230 cm^{-1} (CN), 2944 $–CH_2$ in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.23 (s, 2H, CH_2), 9.11 (s, 1H, -NH-), 9.72 (s, 1H, -NH-), 1.65-1.68 (m, 4H, Ar-H) 2.50-2.53 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 6.94 (dd, J=8, 2H, Ar-H), 7.49 (dd, 2H, J=8, Ar-H) at 4-methoxy phenyl ring. Anal. Calcd. For $C_{18}H_{19}N_3O_2S$: C, 63.32; H, 5.61; N, 12.31. Found: C, 63.23; H, 5.55; N, 12.24. Yield: 74%. m.p. 185-188°C, Mass(M+)-347.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(3-chlorophenyl)amino]acetamide(3f)**

FTIR (KBr, cm^{-1}): 3453 cm^{-1} (-NH-)3277 cm^{-1} (-NH- in amide), 1648 cm^{-1} (in C=O amide), 1580 cm^{-1} (S-C=O in thioether), 757 cm^{-1} (C-S) 2220 cm^{-1} (CN), 2937 $–CH_2$ in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.16 (s, 2H, CH_2), 9.24 (s, 1H, -NH-), 9.96(s, 1H, -NH-), 1.61-1.64 (m, 4H, Ar-H) 2.52-2.55 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 6.92-7.62 (m, 4H, Ar-H) at 3-chloro phenyl ring. Anal. Calcd. For $C_{17}H_{16}ClN_3OS$: C, 59.04; H, 4.66; N, 12.15. Found: C, 58.97; H, 4.57; N, 12.10. Yield: 65%. m.p. 172-175°C, Mass(M+)-345.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(3-methylphenyl)amino]acetamide (3g)**

FTIR (KBr, cm^{-1}): 3470 cm^{-1} (-NH-) 3287 cm^{-1} (-NH- in amide), 1668 cm^{-1} (in C=O amide), 1598 cm^{-1} (S-C=O in thioether), 769 cm^{-1} (C-S) 2207 cm^{-1} (CN), 2941 $–CH_2$ in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.24 (s, 2H, CH_2), 9.29 (s, 1H, -NH-), 9.85(s, 1H, -NH-), 1.67-1.70 (m, 4H, Ar-H) 2.45-2.48 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.04-7.82 (m, 4H, Ar-H) at 3-methyl phenyl ring. Anal. Calcd. For $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.38; H, 5.84; N, 12.85. Yield: 75%. m.p. 214-217°C, Mass(M+)-325.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(2-chlorophenyl)amino]acetamide (3h)**

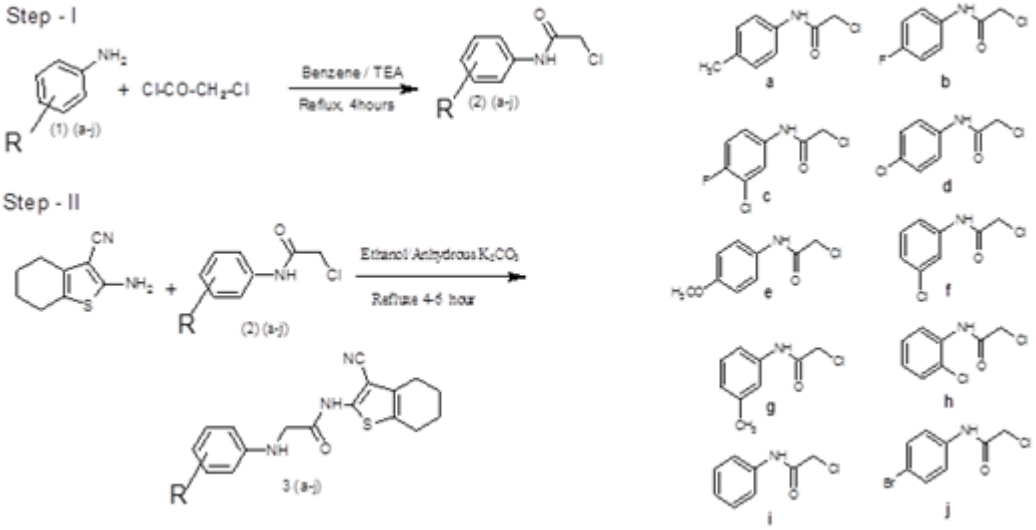
FTIR (KBr, cm^{-1}): 3494 cm^{-1} (-NH-) 3277 cm^{-1} (-NH- in amide), 1660 cm^{-1} (in C=O amide), 1582 cm^{-1} (S-C=O in thioether), 765 cm^{-1} (C-S) 2218 cm^{-1} (CN), 2925 $–CH_2$ in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.30 (s, 2H, CH_2), 9.17 (s, 1H, -NH-), 9.81(s, 1H, -NH-), 1.72-1.75 (m, 4H, Ar-H) 2.56-2.59 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 6.91-7.68 (m, 4H, Ar-H) at 2-chloro phenyl ring. Anal. Calcd. For $C_{17}H_{16}ClN_3OS$: C, 59.04; H, 4.66; N, 12.15. Found: C, 58.97; H, 4.57; N, 12.10. Yield: 63%. m.p. 181-184°C, Mass(M+)-345.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(phenyl)amino]acetamide (3i)**

FTIR (KBr, cm^{-1}): 3471 cm^{-1} (-NH-)3295 cm^{-1} (-NH- in amide), 1643 cm^{-1} (in C=O amide), 1598 cm^{-1} (S-C=O in thioether), 766 cm^{-1} (C-S) 2222 cm^{-1} (CN), 2920 $–CH_2$ in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.27 (s, 2H, CH_2), 9.14 (s, 1H, -NH-), 9.75 (s, 1H, -NH-), 1.71-1.74 (m, 4H, Ar-H) 2.52-2.55 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 6.81-7.62 (m, 5H, Ar-H) at phenyl ring. Anal. Calcd. For $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.48; H, 5.44; N, 13.43. Yield: 67%. m.p. 155-158°C, Mass(M+)-311.

***N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(4-bromophenyl)amino]acetamide (3j)**

FTIR (KBr, cm^{-1}): 3468 cm^{-1} (-NH-)3290 cm^{-1} (-NH- in amide), 1656 cm^{-1} (in C=O amide), 1593 cm^{-1} (S-C=O in thioether), 757 cm^{-1} (C-S) 2227 cm^{-1} (CN), 2932 $–CH_2$ in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.30 (s, 2H, CH_2), 9.26 (s, 1H, -NH-), 9.84 (s, 1H, -NH-), 1.72-1.75 (m, 4H, Ar-H) 2.48-2.51 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.14 (dd, J=8, 2H, Ar-H), 7.85 (dd, 2H, J=8, Ar-H) at 4-bromo phenyl ring. Anal. Calcd. For $C_{17}H_{16}BrN_3OS$: C, 52.31; H, 4.13; N, 10.77. Found C, 52.26; H, 4.08; N, 10.70. Yield: 77%. m.p. 195-198°C, Mass(M+)-389 (Scheme 1).



Scheme 1: Synthesis of *N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-(arylphenyl)acetamido (Where, 2(a-j))

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against Gram positive *Staphylococcus aureus* (MTCC 96) and *Streptococcus pyogenes* (MTCC 442) and Gram negative *Escherichia coli* (MTCC 443) and *Pseudomonas aeruginosa* (MTCC 1688).

The compound 3e with methoxy group was moderately active against both gram positive bacteria *S. aureus* and *S. pyogenes* Compound 3c with chloro and fluoro group was moderately active against *S. aureus* and *E. coli*. Compound 3b with fluoro group was moderately active against *S. aureus* and compound 3j with bromo group was moderately active against *S. pyogenus*. While other compounds showing overage to poor activity and Gram negative bacteria (Table 1).

Table 1: Antibacterial activity

Minimum inhibition concentration					
S. No.	**Code No.**	***Escherichia coli* (MTCC 443)**	***Pseudomonas aeruginosa* (MTCC 1688)**	***Staphylococcus aureus* (MTCC 96)**	***Streptococcus pyogenes* (MTCC 442)**
1	3a	500	500	500	1000
2	3b	500	500	100	500
3	3c	125	500	500	1000
4	3d	250	500	100	500
5	3e	500	500	500	100
6	3f	1000	500	500	1000
7	3g	500	500	250	500
8	3h	250	500	500	250
9	3i	500	250	200	250
10	3j	500	200	0.25	100
Gentamycin		0.05	1	250	0.5
Ampicillin		100	100	50	100
Chloramphenicol		50	50	50	50
Ciprofloxacin		25	25	10	50
Norfloxacin		10	10	10	10

Antifungal activity

The same synthesized compounds were tested for their anti-fungal activity against three different fungal strains *Candida albicans (MTCC* 227), *Aspergillus niger* (MTCC 282), *Aspergillus clavatus* (MTCC 1323).The data of antifungal activity of this series indicated that, compound 3b with fluoro was exhibit very good activity against *A. clavatus*, compound 3c with fluoro and chloro group was exhibit very good activity against *A. niger*. Compound 3j with bromo group was exhibit very good activity against *A. clavatus.* Rest of compounds was not showing potential activity again any species (Table 2).

Table 2: Antifungal activity

Minimal inhibition concentration				
S. No.	**Code No.**	***Candida albicans* (MTCC 227)**	***Aspergillus niger* (MTCC 282)**	***Aspergillus clavatus* (MTCC 1323)**
1	3a	1000	> 1000	> 1000
2	3b	1000	1000	100
3	3c	500	100	> 1000
4	3d	> 1000	> 1000	> 1000
5	3e	500	> 1000	> 1000
6	3f	> 1000	> 1000	1000
7	3g	> 1000	> 1000	> 1000
8	3h	500	> 1000	> 1000
9	3i	> 1000	1000	1000
10	3j	> 1000	500	100
Nystatin		100	100	100
Griseofulvin		500	100	100

CONCLUSION

A series of acetamide derivatives has been successfully synthesized and tested for their anti-microbial activity. 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile is one of the active constituents present in many standard drugs, and is known to increase in pharmacological activity of the molecules as we have already reported its significant activity. The presence of acetamide linkage is also an instrumental in contributing the net biological activity. Herein, we have combined all these two potential unit, that is 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile clubbed 2-chloro-N-(aryl)-acetamides and studied biological behavior of the resultant systems. Overall conclusion placed for synthesized compounds is that most of the compounds shown very good promising activity as compared to standard drug for all representative panel anti-bacterial and antifungal strains.

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