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SYNTHESIS AND CHARACTERIZATION OF N-(4-ACETYL-5-ARYL-4,5-DIHYDRO-1,3,4-THIADIAZOL-2-YL)ACETAMIDE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT

A series ofN-(4-acetyl-5-aryl-4,5-dihydro-1,3,4-thiadiazol-2-yl) acetamide (3a-h) have been synthesized from thiosemicarbazones. The synthesized compounds were characterized by, IR spectra, 1H-NMR and 13C-NMR and screened for antimicrobial activity such as antibacterial and antifungal.

Keywords: Thiazole, Thiosemicarbazone, Antimicrobial

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INTRODUCTION

Thiazoles are nitrogen and sulphur containing heterocyclic compound.Thiazoles and their derivatives are found to be associated with various biological activities such as antifungal , anti-inflammatory activities[1-3] and antibacterial[4-6], anti HIV[7], pesticidal[8], antiprotozoal[9] anticancer[10], [11], antitumor[12], hypertension[13]The synthesis of thiazole derivatives is important for their wide range of pharmaceutical and biological properties.In view of the literature reports, I have designed the synthesis and antimicrobial screening of novel acetylated thiazoles derivatives.Aldehydes on treatment with thiosemicarbazide were converted into thiosemicarbazone, further thiosemicarbazone on reaction with acetic anhydride resulted in N-(4-acetyl-5-aryl-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide (3a-h). The synthesized molecules were supported by IR, 1H-NMR and mass spectral data and screened for antimicrobial activity.

MATERIALS AND METHODS

All melting points were measured in open capillary tubes and are uncorrected. The progress of the reaction was monitored by thin layer chromatography (TLC) and the spots were exposed to iodine vapours for visualization. IR spectra were recorded on Shimadzu FTIR (KBr)-408 spectrophotometer. The ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$/DMSO-d_6 using TMS as internal standard and are given in δ units. The LC-MS spectra were recorded on a WATER, Q-TOF Micossmass

Synthesis of Thiosemicarbazones (2a- h)

A mixture of semithiocarbazide (1mmole), aromatic aldehyde 1 (1mole) and catalytic amount of glacial acetic acid were taken in 20 ml ethanol and refluxed for 4-5 hrs the mixture was poured into cold. The solid separated wasfiltered, washed with water filtered and dried.

Synthesis of 5-aryl-4, 5-dihydro-1,3,4-thiazoles (3a-h)

A mixture of thiosemicarbazone 2a-h(1mmol) and acetic anhydride (1.2mmol) in 10 ml glacial acetic acid was reflux for 1hr and progress of reaction was monitored by TLC After

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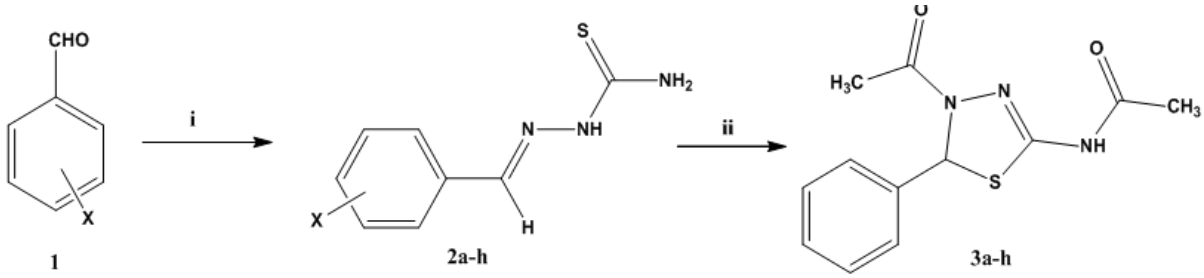
completion of reaction, content was cooled to room temperature. The reaction mixture was poured into ice cold water, separated solid was filtered washed with water and purified by recrystallized from ethanol to afford pure products 3a-h.



Reagents and conditions: i) Thiosemicarbazide, EtOH, reflux. ii) Acetic anhydride/ Glacial acetic acid, reflux for 1hr.

Scheme-1

RESULTS AND DISCUSSION

The title compounds 3a-h was synthesized from differently substituted semithiocarbazone (1a-1h) as shown in scheme 1. **S**emithiocarbazone was treated with acetic anhydride in presence of acetic acid to afford N-(4-acetyl-5-aryl-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide in good yield as solids. The structures of newly synthesized compounds 3a-h were confirmed by IR, ^{1}H-NMR, LC- MS. In IR spectrum, the compound 3a-h exhibited a sharp absorption bands at 1701-1641 cm^{-1} for CO stretching and at 3215 cm^{-1} for NH stretching. The structure of compound 3a-h was confirmed by NMR spectroscopy.

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Table -1. Physical data of synthesized N-(4-acetyl-5-aryl-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide 3a-h

	R-CHO	Molecular F.	M.Wt.	Yield[a](%)	M.P.(^{o}C)	Comp. no.
1	4-Fluoro C_6H_4	$C_{12}H_{12}N_3O_2SF$	280	82	228-230	3a
2	2-OCH_3 C_6H_4	$C_{13}H_{15}N_3O_3S$	293	88	248-250	3b
3	2-naphthyl	$C_{16}H_{15}N_3O_2S$	313	87	230-232	3c
4	2-furyl	$C_{10}H_{11}N_3O_3S$	253	85	176-178	3d
5	3- Cl C_6H_4	$C_{12}H_{12}N_3O_2SCl$	297	90	168-170	3e
6	2-$NO_2C_6H_4$	$C_{12}H_{12}N_4O_4S$	308	82	146-148	3f
7	2-Cl C_6H_4	$C_{12}H_{12}N_3O_2SCl$	297	85	212-214	3g
8	2-OH C_6H_4	$C_{12}H_{13}N_3O_3S$	279	80	214-216	3h

All the synthesized compounds 3a-h was evaluated for antimicrobial activity. The compounds screened for their antibacterial activity againstvarious pathogenic bacteria such as *S. aureus, E. coli and P. vulgaris* by disc diffusion method at 50, 100,150, and 200 microgram per ml conc. Compounds 3a, 3e and 3h showed promising activity against *E. coli and P. vulgaris* and other shows moderate to weak activity against antibacterial stain. These compounds also screened for their antifungal activity against two strains of fungi *A. fumigates and C. albicans*. Compounds 3a, 3f, 3g show considerable potency against A. fumigates while these are moderately active against *C. albicans.*

Spectral analysis

N-(4-Acetyl-5-(4-Fluorophenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide **3a**:

Yield 82%. mp 228-230 ^{0}C

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1H-NMR d : 2.05 (s,3H, –NHCOCH$_3$), 2.20 (s, 3H, –COCH$_3$), 6.80 (s, 1H, H-5), 7.09-7.32 (m,4H, Ar-H), 11.72 (s, 1H, –NH–) IR (KBr) cm^{-1}: 3215 (NH), 1701, 1641(C=O), 1606 (C-N), 1296 (C-S)..Mass EI m/z : 281 [m+1]

N-(4-Acetyl-5-(2-Methoxyphenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide **3b**:

Yield 88%. mp 248-250 ^{0}C

1H-NMR d : 2.00 (s,3H, –NHCOCH$_3$), 2.27 (s, 3H, –COCH$_3$), 3.87 (s, 3H, –OCH$_3$), 6.79 (s, 1H, H-5), 6.86-6.92 (m,2H, Ar-H), 7.02 (d,1H, Ar-H), 7.30 (m,1H, Ar-H), 11.64 (s, 1H, –NH–)

IR (KBr) cm^{-1}: 3211 (NH), 1705, 1641(C=O), 1602 (C-N), 1296 (C-S).

.Mass EI m/z : 294 [m+1]

N-(4-Acetyl-5-(2-napthyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide **3c**:

Yield87%. mp 230-232 ^{0}C.

1H-NMR d : 2.01 (s,3H, –NHCOCH$_3$), 2.34 (s, 3H, –COCH$_3$), 7.48 (s, 1H, H-5), 7.20 (d,1H, Ar-H), 7.45 (t,1H, Ar-H), 7.52-7.61 (m,2H, Ar-H), 7.83 (d,1H, Ar-H), 7.93 (d,1H, Ar-H), 8.04 (d,1H, Ar-H), 11.69 (s, 1H, –NH–)

IR (KBr) cm^{-1}: 3209 (NH), 1708, 1633(C=O), 1593 (C-N), 1286 (C-S).

. Mass EI m/z : 314 [m+1]

N-(4-Acetyl-5-(2-furyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide **3d**:

Yield 85%. mp 176-178^{0}C.

1H-NMR d : 2.06 (s,3H, –NHCOCH$_3$), 2.16 (s, 3H, –COCH$_3$), 6.88 (s, 1H, H-5), 6.30 (d,1H, Ar-H), 6.36 (m,1H, Ar-H), 7.83 (d,1H, Ar-H), 7.55 (d,1H, Ar-H), 11.84 (s, 1H, –NH–)

IR (KBr) cm^{-1}: 3211 (NH), 1699, 1641(C=O), 1610 (C-N), 1288 (C-S).

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.Mass EI m/z: 253 [m]

N-(4-Acetyl-5-(3-Chlorophenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide **3e**:

Yield 90%. mp 168-170 ^{0}C

1H-NMR d : 2.05 (s,3H, –NHCOCH$_3$), 2.22 (s, 3H, –COCH$_3$), 6.80 (s, 1H, H-5), 7.22 (d,1H, Ar-H), 7.28-7.37 (m,3H, Ar-H), 11.74 (s, 1H, –NH–)

IR (KBr) cm^{-1}: 3225 (NH), 1707, 1639(C=O), 1608 (C-N), 1294 (C-S), 1039(-Cl)

.Mass EI m/z: 298 [m+1]

N-(4-Acetyl-5-(2-Nitroyphenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide **3f**:

Yield 82%. mp 246-248 ^{0}C.

1H-NMR d : 2.04 (s,3H, –NHCOCH$_3$), 2.27 (s, 3H, –COCH$_3$), 7.07 (s, 1H, H-5), 7.35 (d,1H, Ar-H), 7.61 (t,1H, Ar-H), 7.80 (t,1H, Ar-H), 8.16 (d,1H, Ar-H), 11.82 (s, 1H, –NH–)

IR (KBr) cm^{-1}: 3232 (NH), 1662, 1622(C=O), 1579 (C-N), 1519, 1342.(NO$_2$), 1290 (C-S)

.Mass EI m/z: 309[m+1]

N-(4-Acetyl-5-(2-Chlorophenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide **3g**:

Yield 95%. mp 212—214 ^{0}C

1H-NMR d : 2.05 (s,3H, –NHCOCH$_3$), 2.22 (s, 3H, –COCH$_3$), 6.80 (s, 1H, H-5), 7.22 (d,1H, Ar-H), 7.28-7.37 (m,3H, Ar-H), 11.74 (s, 1H, –NH–)

IR (KBr) cm^{-1}: 3240 (NH), 1707, 1664(C=O), 1631 (C-N), 1294 (C-S), 1041(-Cl)

Mass EI m/z : 298 [m+1]

N-(4-Acetyl-5-(2-Hydroxyphenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide **3h**

Yield 80%. mp 214-216 ^{0}C

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1H-NMR d : 2.05 (s,3H, –NHCOCH$_3$), 2.22 (s, 3H, –COCH$_3$), 6.80 (s, 1H, H-5), 7.22 (d,1H, Ar-H), 7.28-7.37 (m,3H, Ar-H), 11.74 (s, 1H, –NH–)

IR (KBr) cm^{-1}: 3205 (NH), 1761, 1695(C=O), 1637 (C-N), 1292 (C-S).

Mass EI m/z : 277 [m-2]

CONCLUSION

The heterocyclic compounds containing 1,3,4-thiadiazol possess a wide range of applications in pharmaceutical fields. In this context, above synthesized compounds 2a-h shows a moderate to good antimicrobial activity as compare to standard drugs

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