RESEARCH ARTICLE

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A Facile Synthesis and Antimicrobial Activity of 3-(2-Aroylaryloxy)methyl-5-Mercapto-4-Phenyl-4*H*-1,2,4-Triazole and 2-(2-Aroylaryloxy)methyl-5-N-Phenylamino-1,3,4-Thiadiazole Analogues

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ABSTRACT: Substituted aroylaryloxy acetohydrazides (4a-e) have been synthesized from ethyl aroylaryloxy acetates (3a-e) and condensed with phenyl isothiocyanate to yield corresponding hydrazinecarbothioamide (5a-e). Intramolecular cyclization of 5a-e gave the target compounds, 3-(2-aroylaryloxy)methyl-5-mercapto-4-phenyl-4H-1,2,4-triazoles(6a-e) and 2-(2-aroyl aryloxy)methyl-5-N-phenylamino-1,3,4-thiadiazoles (7a-e) analogues with sodium hydroxide and orthophosphoric acid respectively in excellent yield. Compounds 6a, 6c, 7a and 7c were found to have potent antimicrobial activity.

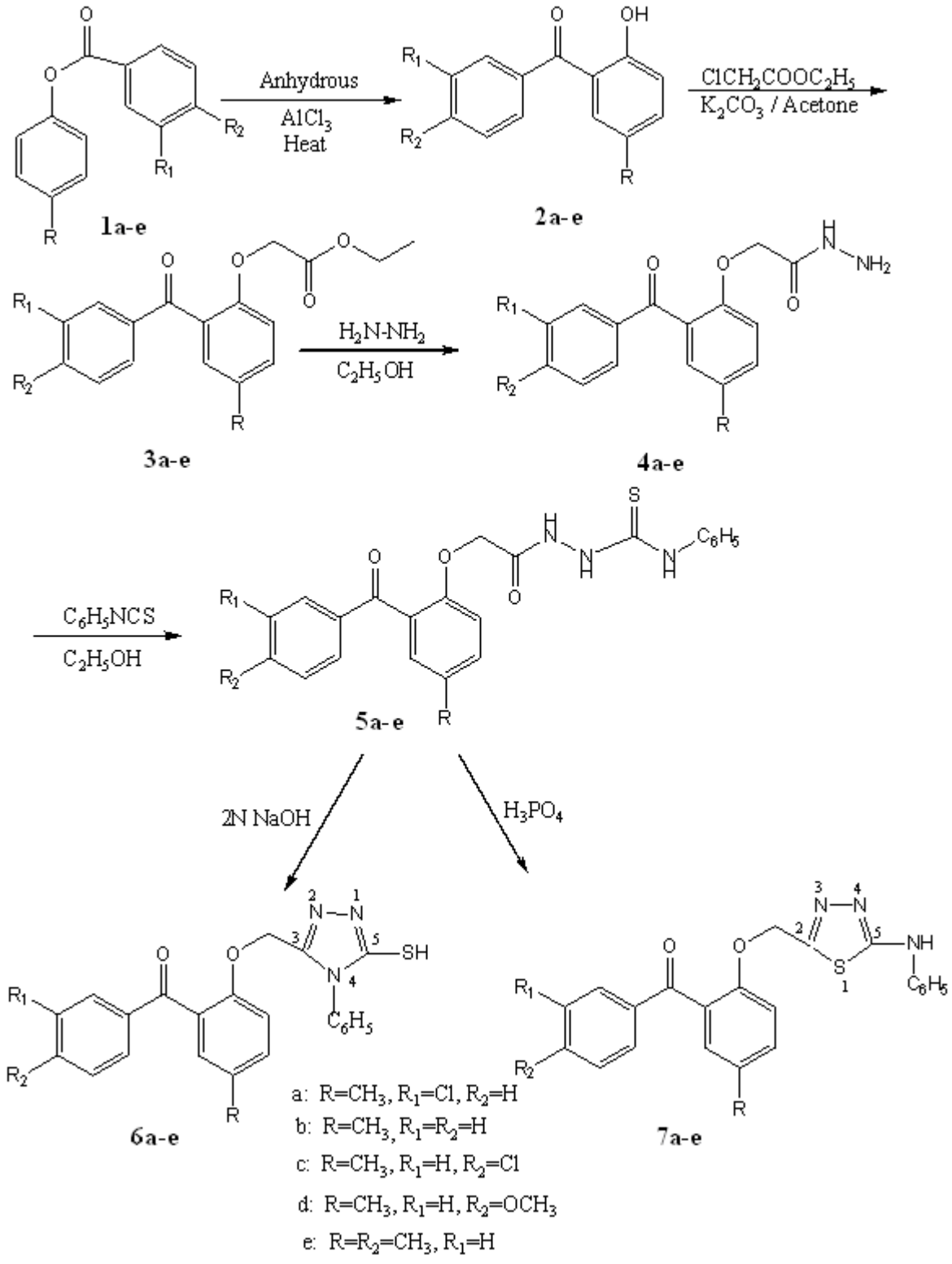
KEYWORDS: triazole, thiadiazole analogues, synthesis, antimicrobial activity.

INTRODUCTION

5-Mercapto-4*H*-1,2,4-triazole and 5-amino-1,3,4-thiadiazole analogues possess wide spectrum of biological activity such as hypoglycemic,[1,2] bacteriostatic,[3] diuretic,[2] antiviral[4] and antifungal[5] activities. The 5-amino-1,3,4-thiadiazole analogues were also reported to be active against vaccinia.[6] Bossche et al[7] have reported that the major effect of triazoles on fungi is inhibition of sterol 14-α-demethylase, a microsomal cytochrome P-450 dependent enzyme system. Triazoles thus impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14-α-methylsterols. These methylsterols may disrupt the close packing of acyl chains of phospholipids impairing the functions of certain membrane bound enzyme systems such as adenosine triphosphatase and enzymes of the electron transport system and thus inhibiting growth of the fungi. In addition to this, biological activities of benzophenone analogues have been reported as an antiallergic, antiinflammatory, antiasthmatic and anaphylactic agents.[8,9] These analogues inhibit the release of leukotrienes C_4 and D_4 in *vitro* from sensitized guinea pig chopped lungs. Some of the analogues inhibited the release of leukotrienes from passively sensitized human chopped lungs. These analogues are evaluated as inhibitors of HIV reverse transcriptase (RT) and the growth of HIV in MT-4 cells. The structural activity relationship indicated that the major interactions of benzophenone derivatives with the RT enzyme are through hydrogen bonding with benzophenone carbonyls and pi-orbital interactions with the benzophenone nucleus.[10] In combination with the antimicrobial activity of 5-mercapto-4*H*-1,2,4-triazole, 5-amino-1,3,4-thiadiazole and benzophenone analogues, it was considered worthwhile to incorporate the heterocyclic moieties to the benzophenone nucleus. In view of these observations, synthesis of a series of 5-mercapto-4*H*-1,2,4-triazoles (**6a-e**) and 5-amino-1,3,4-thiadiazoles (**7a-e**) analogues have been undertaken and screened for their antimicrobial activity and some of the chloro substituted derivatives such as **6a, 6c, 7a** and **7c** were found to be most potent.

MATERIALS AND METHODS

The strategy employed in the synthesis of desired compounds is as follows (scheme 1). Substituted phenyl benzoates (**1a-e**) on Fries rearrangement using anhydrous aluminum chloride gave corresponding substituted 2-hydroxybenzophenones (**2a-e**) in excellent yield[11,12] According to literature survey **2a**[11] and **2b**[12] are known compounds. Condensation of **2a-e** with ethyl chloroacetate in the presence of anhydrous potassium carbonate in dry acetone gave ethyl (2-aroylaryloxy)acetates (**3a-e**),[13] which on


Anhydrous
AlCl3
Heat
ClCH2COOC2H5
K2CO3 / Acetone
1a-e
2a-e
H2N-NH2
C2H5OH
3a-e
4a-e
C6H5NCS
C2H5OH
5a-e
2N NaOH
H3PO4
6a-e
7a-e
a: R=CH3, R1=Cl, R2=H
b: R=CH3, R1=R2=H
c: R=CH3, R1=H, R2=Cl
d: R=CH3, R1=H, R2=OCH3
e: R=R2=CH3, R1=H

Scheme 1

treatment with 80% hydrazine hydrate in ethanol yielded the respective 2-(2-aroylaryloxy)aceto hydrazides (**4a-e**).[14] **4a-e** with phenyl isothiocyanate in dry ethanol gave 2-[2-(aroylaryloxy)acetyl]-N-phenylhydrazinecarbothioamides (**5a-e**),[14] which on cyclization with 2N sodium hydroxide and anhydrous orthophosphoric acid gave 3-(2-aroylaryloxy)methyl-5-mercapto-4-phenyl-4*H*-1,2,4-triazoles (**6a-e**)[15] and 2-(2-aroylaryloxy)methyl-5-N-phenylamino-1,3,4-thiadiazoles (**7a-e**)[14] analogues respectively in excellent yield.

Antimicrobial Activity

All these compounds were screened for their antimicrobial activity against three pathogenic bacteria viz., *Bacillus cereus, Staphylococcus aureus and Escherichia coli* and three cultures viz., *Penicillium nigricans, Aspergillus fumigatus and Fusarium solani*. The standard drugs used were Norfloxacin and Griseofulvin. The tests were carried out with the title compounds by the cup plate method[16] with 20 mg of the substance in 0.1 ml of dimethylformamide. The total area of inhibition was calculated by the area of inhibition, in comparison with the reference drug, as follows:

Relative % inhibition = 100(X-Y)/(Z-Y)
X= total area of inhibition in test plate.
Y= total area of inhibition in solvent (DMF) plate.
Z= total area of inhibition in reference plate.
Area of inhibition = πr^2
r = radius of inhibition zone in test, solvent and reference plates.

Preparation

*General procedure for the preparation of substituted 2-hydroxybenzophenones (**2a-e**):*

In a typical procedure, 4-methylphenyl 3-chlorobenzoate (**1a** 5 g, 0.02 mol) was well mixed with the anhydrous aluminum chloride (4.65 g, 0.03 mol) and heated at 120 °C for 10 min then at 140 °C for 15 min. At the end of this period the solution was cooled and decomposed by acidified ice-cold water and filtered. The residual solid was crushed into powder, extracted with 10% sodium hydroxide (3×30 ml) and the basic aqueous solution was neutralized with 10% hydrochloric acid. The product was extracted into ether and the ether layer was washed well with saturated sodium chloride solution. Evaporation of ether after drying over anhydrous sodium sulphate followed by recrystallization from ethanol gave a pale yellow crystalline solid of (2-hydroxy-5-methylphenyl)-(3- chlorophenyl)methanone (**2a**) in 85% (4.25 g) yield. General procedure for the preparation of ethyl (2-aroylaryloxy)acetates (**3a-e**):

In a typical procedure, a mixture of **2a** (5 g, 0.02 mol) and ethyl chloroacetate (2.4 g, 0.02 mol) in dry acetone (60 ml) and anhydrous potassium carbonate (2.8 g, 0.02 mol) was refluxed for 8 hrs then cooled and the solvent removed under reduced pressure. The residual mass was triturated with cold water to remove potassium carbonate and extracted with ether (3×50 ml) and the ether layer was washed with 10% sodium hydroxide solution (3×30 ml) followed by water (3×30 ml) and then dried over anhydrous sodium sulphate and evaporated to dryness to get crude solid, which on recrystallization with ethanol gave ethyl [2-(3-chlorobenzoyl)-4-methylphenoxy]acetate **(3a)** in 81% (5.39 g) yield as a white crystalline solid.

*General procedure for the preparation of 2-(2-aroylaryloxy)acetohydrazides (**4a-e**):*

In a typical procedure, to 3a (2 g, 6 mmol) in ethanol (10 ml), 80% hydrazine hydrate (0.3 g, 6 mmol) was added in drops and stirred for 1 hr at room temperature. A white solid separated, which on recrystallization with ethanol gave 2-[2-(3-chlorobenzoyl)-4-methylphenoxy]acetohydrazide (**4a**) as white crystalline solid in 75% (1.43 g) yield.

*General procedure for the preparation of 2-[2-(aroylaryloxy)acetyl]-N-phenylhydrazine-carbothioamides (**5a-e**):*

In a typical procedure, a mixture of phenyl isothiocyanate (0.5 g, 3.7 mmol) and **4a** (1.17g, 3.6 mmol) in dry ethanol (20 ml) was refluxed with stirring for 4 hrs; the mixture was cooled, filtered, washed with ethanol, dried and recrystallized with ethanol to give 2-{[2-(3-chlorobenzoyl)-4-methylphenoxy]acetyl}-N-phenylhydrazinecarbothioamide (**5a)** as yellow needles in 70% (0.49 g) yield.

*General procedure for the preparation of 3-(2-aroylaryloxy)methyl-5-mercapto-4-phenyl-4H-1,2,4-triazoles (**6a-e**):*

In a typical procedure, **5a** (0.5 g, 1.14 mmol) and 2N sodium hydroxide solution (10 ml) was refluxed for 3 hrs. The cooled reaction mixture was acidified with 2N HCl (pH 4). The white precipitate was filtered, washed with water, dried and recrystallized with ethanol to give 3-[2-(3-chlorobenzoyl)-4-methyl-phenoxy]methyl-5-mercapto-4-phenyl-4*H*-1,2,4-triazole **(6a)** as white solid in 73% (0.39 g) yield.

*General procedure for the preparation of 2-(2-aroylaryloxy)methyl-5-N-phenyl amino-1,3,4-thiadiazoles (**7a-e**):*

In a typical procedure, **5a** (0.5 g, 1.14 mmol) was added gradually to anhydrous orthophosphoric acid

(10 ml) in about 5 min. The reaction mixture was heated in an oil bath at 120 °C for 2 hrs. The slurry thus obtained was poured on crushed ice. The solid was filtered, washed with cold water, dried and recrystallized with ethanol to give 2-[2-(3-chlorobenzoyl)-4-methylphenoxy]methyl-5-N-phenylamino-1,3,4-thiadiazole (**7a**) as brown solid in 70% (0.39 g) yield.

The physical data and spectral data of all the compounds prepared are summarized in Table 1 and Table 2 respectively.

Results and Discussion

Experimental Spectrum

The structures of all compounds were supported by IR, NMR and mass spectral data. The IR spectra of compounds **6a-e** showed bands at 1605-1620 (C=N) & 2500-2575 cm^{-1} (S-H) and **7a-e** at 745-760 (C-S-C) & 1615-1625 cm^{-1}(C=N). The absence of a band in **6a-e** and **7a-e** at 1230-1245 cm^{-1}(C=S), which is characteristic of carbothioamides, confirms the transformation of **5a-e** to **6a-e** and **7a-e**. ^{1}H NMR of **6a-e** showed a singlet at δ 9.9-10.3 for SH protons and for **7a-e** a broad singlet at δ 4.8-4.9 (D_2O exchanged) for NH. The analogues of 5-mercapto-4*H*-1,2,4-triazole and 5-amino-1,3,4-thiadiazole gave significantly stable molecular ion peak with relative

Table 1. Yield and physical data of all compounds prepared.

Product	Yield	mp	lit.mp	Mol	Elemental analysis (Found)				
	%	°C	°C	Formular	C	H	Cl	N	S
2a	85	71-73	72	$C_{14}H_{11}ClO_2$	68.15 (68.11)	4.46 (4.43)	14.40 (14.38)	-	-
2b	83	81-83	85	$C_{14}H_{12}O_2$	79.24 (79.20)	5.66 (5.63)	-	-	-
2c	72	78-80	-	$C_{14}H_{11}ClO_2$	68.15 (68.13)	4.46 (4.44)	14.40 (14.39)	-	-
2d	75	75-78	-	$C_{15}H_{14}O_3$	73.38 (73.36)	5.78 (5.75)	-	-	-
2e	77	82-83	-	$C_{15}H_{14}O_2$	79.64 (79.60)	6.19 (6.15)	-	-	-
3a	81	65-67	-	$C_{18}H_{17}ClO_4$	64.96 (64.92)	5.11 (5.08)	10.67 (10.63)	-	-
3b	79	60-63	-	$C_{18}H_{18}O_4$	72.48 (72.44)	6.04 (6.0)	-	-	-
3c	70	62-65	-	$C_{18}H_{17}ClO_4$	64.96 (64.94)	5.11 (5.09)	10.67 (10.65)	-	-
3d	72	58-60	-	$C_{19}H_{20}O_5$	69.51 (69.48)	6.09 (6.05)	-	-	-
3e	79	57-59	-	$C_{19}H_{20}O_4$	73.07 (73.04)	6.41 (6.38)	-	-	-
4a	75	177-80	-	$C_{16}H_{15}ClN_2O_3$	60.28 (60.24)	4.70 (4.67)	11.14 (11.11)	8.79 (8.75)	-
4b	73	179-81	-	$C_{16}H_{16}N_2O_3$	67.60 (67.57)	5.63 (5.60)	-	9.85 (9.81)	-
4c	68	182-85	-	$C_{16}H_{15}ClN_2O_3$	60.28 (60.25)	4.70 (4.68)	11.14 (11.12)	8.79 (8.77)	-
4d	65	175-77	-	$C_{17}H_{18}N_2O_4$	64.96 (64.93)	5.73 (5.70)	-	8.91 (8.88)	-
4e	71	186-88	-	$C_{17}H_{18}N_2O_3$	68.45 (68.41)	6.04 (6.0)	-	9.39 (9.35)	-

Table 1. Yield and physical data of all compounds prepared (cont.).

Product	Yield	mp	lit.mp	Mol	Elemental analysis (Found)				
	%	°C	°C	Formular	C	H	Cl	N	S
5a	70	210-13	-	$C_{23}H_{20}ClN_3O_3S$	60.85 (60.82)	4.41 (4.37)	7.82 (7.79)	9.26 (9.22)	7.05 (7.02)
5b	68	205-08	-	$C_{23}H_{21}N_3O_3S$	65.87 (65.83)	5.01 (4.97)	-	10.02 (10.0)	7.63 (7.59)
5c	63	199-02	-	$C_{23}H_{20}ClN_3O_3S$	60.85 (60.81)	4.41 (4.38)	7.82 (7.78)	9.26 (9.23)	7.05 (7.01)
5d	60	200-03	-	$C_{24}H_{23}N_3O_4S$	64.14 (64.10)	5.12 (5.09)	-	9.35 (9.31)	7.12 (7.08)
5e	68	206-09	-	$C_{24}H_{23}N_3O_3S$	66.51 (66.48)	5.31 (5.28)	-	9.69 (9.66)	7.39 (7.35)
6a	73	120-23	-	$C_{23}H_{18}ClN_3O_2S$	63.37 (63.35)	4.13 (4.10)	8.15 (8.11)	9.64 (9.61)	7.34 (7.32)
6b	65	125-28	-	$C_{23}H_{19}N_3O_2S$	68.82 (68.79)	4.73 (4.70)	-	10.47 (10.45)	7.98 (7.95)
6c	60	121-24	-	$C_{23}H_{18}ClN_3O_2S$	63.37 (63.34)	4.13 (4.10)	8.15 (8.12)	9.64 (9.61)	7.34 (7.31)
6d	57	119-22	-	$C_{24}H_{21}N_3O_3S$	66.82 (66.79)	4.87 (4.83)	-	9.74 (9.72)	7.42 (7.39)
6e	69	125-28	-	$C_{24}H_{21}N_3O_2S$	69.39 (69.35)	5.06 (5.03)	-	10.12 (10.10)	7.71 (7.68)
7a	70	130-33	-	$C_{23}H_{18}ClN_3O_2S$	63.37 (63.34)	4.13 (4.11)	8.15 (8.13)	9.64 (9.63)	7.34 (7.30)
7b	63	125-27	-	$C_{23}H_{19}N_3O_2S$	68.82 (68.80)	4.73 (4.71)	-	10.47 (10.44)	7.98 (7.94)
7c	59	120-22	-	$C_{23}H_{18}ClN_3O_2S$	63.37 (63.35)	4.13 (4.09)	8.15 (8.13)	9.64 (9.62)	7.34 (7.30)
7d	55	128-30	-	$C_{24}H_{21}N_3O_3S$	66.82 (66.78)	4.87 (4.84)	-	9.74 (9.71)	7.42 (7.38)
7e	68	133-36	-	$C_{24}H_{21}N_3O_2S$	69.39 (69.36)	5.06 (5.04)	-	10.12 (10.09)	7.71 (7.69)

intensity ranging from 65-76% and 24-37% respectively.

Antibacterial Activity

The results of these preliminary screening studies are qualitative in nature. Compounds **6a, 6c, 7a** and **7c** have shown growth inhibitory action more than or equal to reference drug Norfloxacin against *Bacillus cereus, Staphylococcus aureus* and *Escherichia coli,* indicating that it is the presence of chlorine which enhance the inhibitory activity. Interestingly, compound **6a** with a chloro group on meta position in benzophenone moiety has shown more than 1.5 times growth inhibitory action and **6c** with a chloro group on para position has shown 2.0 times higher than the reference drug against *Escherichia coli.* Compound **7a** with chloro group on meta position and **7c** with chloro group on para position have shown activity 1.3 times higher and equal to the reference drug against *Bacillus cereus* respectively**.** Compounds **6b, 6e, 7b** and **7e** with methyl group on para position and compounds **6d** and **7d** with methoxy group on para position have shown weak to moderate activity against all pathogenic bacteria. It is worth noting that the presence of chloro group is more significant than alkyl and alkoxy group to enhance the activity. The results are summarized in Table 3.

Antifungal Activity

In case of antifungal activity once again the

Table 2. Spectral data of all compounds prepared.

Product	IR (Nujol) cm^{-1}	^1H NMR ($CDCl_3$) ppm (δ)	Mass Spectra m/z (Relative intensity)
2a	1673 (C=O), 3550-3640 (OH)	2.2 (s, 3H, CH_3), 7.0-7.65 (m, 7H, Ar-H), 9.65 (bs, 1H, OH)	246 (M^+, 88), 245 (100), 135 (62), 139 (37), 111 (57)
2b	1670 (C=O), 3545-3649 (OH)	2.3 (s, 3H, CH_3), 7.1-7.7 (m, 8H, Ar-H), 9.8 (bs, 1H, OH)	212 (M^+, 87), 211 (100), 135 (60), 105 (35), 77 (56)
2c	1675 (C=O), 3555-3645 (OH)	2.15 (s, 3H, CH_3), 7.2-7.8 (m, 7H, Ar-H), 9.7 (bs, 1H, OH)	246 (M^+, 85), 245 (100), 135 (61), 139 (35), 111 (55)
2d	1668 (C=O), 3540-3650 (OH)	2.32 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3) 7.1-7.75 (m, 7H, Ar-H), 9.6 (bs, 1H, OH)	242 (M^+, 83), 241 (100), 135 (56), 107 (52)
2e	1658 (C=O), 3535-3645 (OH)	2.3-2.35 (d, 6H, $2CH_3$), 7.0-7.7 (m, 7H, Ar-H), 9.5 (bs, 1H, OH)	226 (M^+, 85), 225 (100), 135 (58), 119 (52), 91(53)
3a	1670 (C=O), 1735 (ester, C=O)	1.2 (t, 3H, CH_3 of ester), 2.3 (s, 3H, CH_3), 4.2 (q, 2H, CH_2 of ester), 4.45 (s, 2H, OCH_2), 7.2-7.6 (m, 7H, Ar-H)	332 (M^+, 62), 259 (12), 245(12), 221 (100), 193 (6), 139 (39), 111 (34)
3b	1664 (C=O), 1760 (ester, C=O)	1.2 (t, 3H, CH_3 of ester), 2.3 (s, 3H, CH_3), 4.1 (q, 2H, CH_2 of ester), 4.5 (s, 2H, OCH_2), 7.1-7.7 (m, 8H, Ar-H)	298 (M^+, 60), 225 (10), 221(100), 211 (10), 193 (5), 105 (36), 77 (31)
3c	1675 (C=O), 1740 (ester, C=O)	1.22 (t, 3H, CH_3 of ester), 2.35 (s, 3H, CH_3), 4.2 (q, 2H, CH_2 of ester), 4.5 (s, 2H, OCH_2), 7.2-7.7 (m, 7H, Ar-H)	332 (M^+, 61), 259 (11), 245 (11), 221 (100), 193 (5), 139 (37), 111 (32)
3d	1660 (C=O), 1730 (ester, C=O)	1.2 (t, 3H, CH_3 of ester), 2.25 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.2 (q, 2H, OCH_2 of ester), 4.42 (s, 2H, CH_2), 7.0-7.6 (m, 7H, Ar-H)	328 (M^+, 59), 255 (9), 241 (9), 221 (100), 193 (5), 135 (35), 107 (29)
3e	1665 (C=O), 1740 (ester, C=O)	1.2 (t, 3H, CH_3 of ester), 2.3-2.35 (d, 6H, $2CH_3$), 4.25 (q, 2H, CH_2 of ester), 4.45 (s, 2H, OCH_2), 7.2-7.8 (m, 7H, Ar-H)	312 (M^+, 64), 239 (14), 225 (14), 221 (100), 193 (8), 119 (40), 91 (36)
4a	1620 (C=O), 1655 (amide, C=O), 3110-3215 (NH-NH_2)	2.3 (s, 3H, CH_3), 3.7 (bs, 2H, NH_2), 4.5 (s, 2H, OCH_2), 7.1-7.6 (m, 7H, Ar-H), 9.25 (bs, 1H, CONH)	318 (M^+, 47), 207 (100), 179 (12), 139 (50), 111 (30)
4b	1615 (C=O), 1650 (amide, C=O), 3105-3210 (NH-NH_2)	2.25 (s, 3H, CH_3), 3.55 (bs, 2H, NH_2), 4.5 (s, 2H, OCH_2), 7.2-7.7 (m, 8H, Ar-H), 9.2 (bs, 1H, CONH)	284 (M^+, 44), 207 (100), 179 (10), 105 (48), 77 (26)

Note: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet.

Table 2. Spectral data of all compounds prepared (Cont.).

Product	IR (Nujol) cm^{-1}	^1H NMR ($CDCl_3$) ppm (δ)	Mass Spectra m/z (Relative intensity)
4c	1625 (C=O), 1660 (amide, C=O), 3115-3220 ($NH-NH_2$)	2.25 (s, 3H, CH_3), 3.6 (bs, 2H, NH_2), 4.55 (s, 2H, OCH_2), 7.1-7.7 (m, 7H, Ar-H), 9.3 (bs, 1H, CONH)	318 (M^+, 46), 207 (100), 179 (11), 139 (49), 111 (29)
4d	1610 (C=O), 1645 (amide, C=O), 3100-3205 ($NH-NH_2$)	2.2 (s, 3H, CH_3), 3.5 (bs, 2H, NH_2), 3.9 (s, 3H, OCH_3), 4.55 (s, 2H, OCH_2), 7.2-7.9 (m, 7H, Ar-H), 9.4 (bs, 1H, CONH)	314 (M^+, 42), 207 (100), 179 (9), 135 (47), 107 (26)
4e	1630 (C=O), 1670 (amide, C=O), 3120-3220 ($NH-NH_2$)	2.2-2.3 (d, 6H, $2CH_3$), 3.55 (bs, 2H, NH_2), 4.6 (s, 2H, OCH_2), 7.2-7.8 (m, 7H, Ar-H), 9.35 (bs, 1H, CONH)	298 (M^+, 48), 207 (100), 179 (13), 119 (52), 91 (32)
5a	1660 (C=O), 1700 (amide, C=O), 1235 (C=S), 3200-3300 (NH-NH, NH)	2.35 (s, 3H, CH_3), 4.6 (s, 2H, OCH_2), 7.0–7.9 (m, 12H, Ar-H), 9.5–9.8 (bs, 2H, NHCSNH), 10.1 (s, 1H, CONH)	453 (M^+, 5), 361 (7), 317 (19), 194 (25), 164 (20), 152 (24), 135 (100), 111 (47), 93 (26), 77 (24)
5b	1670 (C=O), 1720 (amide, C=O), 1240 (C=S), 3210-3310 (NH-NH, NH)	2.3 (s, 3H, CH_3), 4.65 (s, 2H, OCH_2), 7.1–8.0 (m, 13H, Ar-H), 9.5–9.7 (bs, 2H, NHCSNH), 10.2 (s, 1H, CONH)	419 (M^+, 4), 372 (6), 283 (17), 194 (23), 164 (18), 152 (22), 135 (100), 93 (24), 77 (24)
5c	1665 (C=O), 1705 (amide, C=O), 1230 (C=S), 3205-3305 (NH-NH, NH)	2.3 (s, 3H, CH_3), 4.6 (s, 2H, OCH_2), 7.1–7.9 (m, 12H, Ar-H), 9.6–9.8 (bs, 2H, NHCSNH), 10.1 (s, 1H, CONH)	453 (M^+, 4), 361 (6), 317 (18), 194 (23), 164 (19), 152 (22), 135 (100), 111 (46), 93 (25), 77 (22)
5d	1655 (C=O), 1700 (amide, C=O), 1230 (C=S), 3215-3310 (NH-NH, NH)	2.3 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 4.6 (s, 2H, OCH_2), 7.1–7.95 (m, 12H, Ar-H), 9.6–9.8 (bs, 2H, NHCSNH), 10.2 (s, 1H, CONH)	449 (M^+, 3), 357 (4), 313 (17), 194 (22), 164 (18), 152 (22), 135 (100), 107 (44), 93 (24), 77 (22)
5e	1675 (C=O), 1725 (amide, C=O), 1245 (C=S), 3215-3315 (NH-NH, NH)	2.25-2.3 (d, 6H, $2CH_3$), 4.65 (s, 2H, OCH_2), 7.1–8.1 (m, 13H, Ar-H), 9.5–9.8 (bs, 2H, NHCSNH), 10.25 (s, 1H, CONH)	433 (M^+, 6), 341 (8), 297 (20), 194 (20), 164 (21), 152 (25), 135 (100), 91 (27), 77 (25)
6a	1610 (C=N), 1640 (C=O), 2500-2550 (S-H)	2.2 (s, 3H, CH_3), 4.65 (s, 2H, OCH_2), 7.2–7.8 (m, 12H, Ar-H), 10.2 (s, 1H, SH)	435 (M^+, 72), 407 (21) 376 (25), 245 (35), 149 (32), 139 (100), 91 (31)
6b	1620 (C=N), 1650 (C=O), 2510-2550 (S-H)	2.25(s, 3H, CH_3), 4.55 (s, 2H, OCH_2), 7.3–8.05 (m, 13H, Ar-H), 10.0 (s, 1H, SH)	401(M^+, 76), 373 (24) 342 (28), 251 (37), 149 (35), 105 (100), 91 (30)
6c	1615 (C=N), 1655 (C=O), 2505-2550 (S-H)	2.3 (s, 3H, CH_3), 4.45 (s, 2H, OCH_2), 7.1–8.0 (m, 12H, Ar-H), 10.3 (s, 1H, SH)	435(M^+, 70), 407 (20) 376 (24), 245 (33), 149 (31), 139 (100), 91 (30)

Note: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet.

Table 2. Spectral data of all compounds prepared (Cont.).

Product	IR (Nujol) cm^{-1}	^1H NMR ($CDCl_3$) ppm (δ)	Mass Spectra m/z (Relative intensity)
6d	1605 (C=N), 1665 (C=O), 2525-2575 (S-H)	2.2 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 4.5 (s, 2H, OCH_2), 7.0–7.9 (m, 12H, Ar-H), 9.9 (s, 1H, SH)	431(M^+, 69), 403 (20) 372 (21), 281 (32), 149 (32), 135 (100), 91 (29)
6e	1620 (C=N), 1670 (C=O), 2535-2570 (S-H)	2.25-2.3 (d, 6H, $2CH_3$), 4.45 (s, 2H, OCH_2), 7.1–8.1 (m, 12H, Ar-H), 9.95 (s, 1H, SH)	415(M^+, 65), 387 (18) 356 (21), 265 (31), 149 (30), 119 (100), 91 (29)
7a	750 (C-S-C), 1620 (C=N), 1650 (C=O), 3150 (NH)	2.35 (s, 3H, CH_3), 4.6 (s, 2H, OCH_2), 4.85 (bs, 1H, NH), 7.02–7.8 (m, 12H, Ar-H)	436 (M^+, 30), 407 (40), 317 (75), 285 (30), 152 (35), 139 (100)
7b	755 (C-S-C), 1625 (C=N), 1655 (C=O), 3155 (NH)	2.3 (s, 3H, CH_3), 4.6 (s, 2H, OCH_2), 4.9 (bs, 1H, NH), 7.0–7.9 (m, 13H, Ar-H)	401 (M^+, 37), 373 (46), 283(78), 251 (35), 152 (38), 105 (100)
7c	760 (C-S-C), 1625 (C=N), 1645 (C=O), 3155 (NH)	2.25 (s, 3H, CH_3), 4.5 (s, 2H, OCH_2), 4.8 (bs, 1H, NH), 7.0–7.9 (m, 12H, Ar-H)	436 (M^+, 35), 407 (44), 317(77), 285 (34), 152 (36),139 (100)
7d	750 (C-S-C), 1615 (C=N), 1640 (C=O), 3140 (NH)	2.3 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 4.5 (s, 2H, OCH_2), 4.85 (bs, 1H, NH), 7.1–7.9 (m, 12H, Ar-H)	431 (M^+, 28), 403 (36), 312(70), 280 (27), 152 (31), 135 (100)
7e	745 (C-S-C), 1625 (C=N), 1640 (C=O), 31645 (NH)	2.2-2.3 (d, 6H, $2CH_3$), 4.5 (s, 2H, OCH_2), 4.85 (bs, 1H, NH), 7.1–7.9 (m, 12H, Ar-H)	415 (M^+, 24), 387 (32), 296 (67), 265 (25), 152 (27), 119 (100)

Note: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet.

Table 3. Results of antibacterial activity.[a]

Comp.	*Bacillus cereus*		*Staphylococcus aureus*		*Escherichia coli*	
	Area of inhibition mm^2	Relative % of inhibition	Area of inhibition mm^2	Relative % of inhibition	Area of inhibition mm^2	Relative % of inhibition
6a	50.00	100.00	48.00	96.00	176.00	163.00
6b	-	-	-	-	39.00	25.00
6c	46.00	92.00	38.00	69.00	201.00	200.00
6d	28.00	41.00	38.00	69.00	38.00	25.00
6e	30.00	60.00	-	-	28.00	15.00
7a	63.00	135.00	50.00	100.00	100.00	99.00
7b	19.00	38.00	-	-	63.00	50.00
7c	52.00	104.00	42.00	84.00	96.00	95.00
7d	38.00	69.00	19.00	38.00	50.00	37.00
7e	24.00	48.00	-	-	-	-

[a]Relative inhibition of reference drugs is taken as 100%

Table 4. Results of antifungal activity.[a]

Comp.	*Penicillium nigricans*		*Aspergillus fumigatus*		*Fusarium solani*	
	Area of inhibition mm^2	Relative % of inhibition	Area of inhibition mm^2	Relative % of inhibition	Area of inhibition mm^2	Relative % of inhibition
6a	78.00	100.00	50.00	100.00	-	-
6b	-	-	-	-	-	-
6c	78.00	100.00	78.00	175.00	28.28	41.00
6d	38.00	39.00	28.00	48.00	-	-
6e	28.00	23.00	-	-	38.00	68.00
7a	113.00	152.00	50.00	100.00	-	-
7b	-	-	-	-	-	-
7c	95.00	124.00	48.00	96.00	-	-
7d	38.00	39.00	28.00	41.00	19.00	18.75
7e	132.00	182.00	30.00	60.00	-	-

[a]Relative inhibition of reference drugs is taken as 100%

compounds having chloro substituent viz., **6a, 6c, 7a** and **7c** have shown considerable antifungal activity more than or equal to reference drug Griseofulvin against *Penicillium nigricans* and *Aspergillus fumigatus* Compounds **6a** and **7a** with chloro group on meta position have shown equal activity against *Aspergillus fumigatus* compared to the standard drug. Compound **7a** has shown 1.5 times more activity than the reference drug against *Penicillium nigricans*. Compounds **6c** and **7c** with chloro group on para position have shown growth inhibitory action equal and more compared to the standard drug against *Penicillium nigricans* respectively. Also compound **6c** has shown more than 1.5 times growth activity and **7c** equal activity compared to the reference drug against *Aspergillus fumigatus*. Compounds **6b** and **7b** with methyl group on para position have not shown activity against all the strains. On the contrary, compound **7e** with two methyl substituents on two Phenyl rings of benzophenone moiety has shown enhanced antifungal activity against *Penicillium nigricans*. But no compound has shown considerable antifungal activity against *Fusarium solani*. The results are summarized in Table 4.

Conclusion

In conclusion our study shows a strong evidence for the antimicrobial activity of chloro substituted triazole and thiadiazole linked benzophenones. It is interesting and significant to note from the data in Tables 3 and 4 that compounds **6a, 6c, 7a** and **7c** with chloro group exhibit in general growth inhibitory activity more relevant than that of the reference compound and triazole-linked benzophenones **6a** and **6c** has shown higher degree of antimicrobial activity compared to thiadiazole-linked benzophenones **7a** and **7c.** Compounds **6b, 6e, 7b** and **7e** with methyl group and **6d** and **7d** with methoxy group exhibit in general growth inhibitory activity less compared to that of reference compound. From these observations, with slight modification in the structure one can plan for the drug design.

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