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Synthesis and antimicrobial activities of 1-Naphthylamine based acetophenone semicarbazones

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Abstract

A series of novel highly functionalized novel para-amino acetophenone semicarbazones derivative have been synthesized from 1-naphthylamine, sodium cyanate, hydrazine hydrate in good-to-excellent yield. The synthesized compounds were characterized and screened for their *in-vitro* antibacterial and antifungal activities by disc diffusion and twofold serial dilution method. The prepared compounds were tested against the standard strains viz. *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *E. faecalis* and the yeasts *Candida albicans*, *Candida tropicalis* & *Candida krusie*. The result of antimicrobial assay revealed the presence of excellent activity against gram positive i.e. *S.aureus* compared to gram negative *E.coli* and *P.aeruginosa*. Antifungal test revealed moderate activity against different *candida* strains.

Keywords: Semicarbazones, antimicrobials, Disc diffusion, MIC

Introduction

Resistance towards microbes creates a serious problem since last three decades. So the need of an hour is to search new novel antimicrobial (Cunha, 1998). Semicarbazides have been known to have significant biological activity against important pathogens. Semicarbazones are among the most relevant nitrogen-oxygen donor ligands (Gingrass et al., 1961). A good deal of work has been reported on the preparation and structural investigation of semicarbazones and their complexes. Semicarbazone and their derivatives are of much interest because of wide spectrum of antimicrobial activities (Dogan et al., 1999; Pandeya et al., 1993). In addition thio- and semicarbazones possess a wide range of bioactivities, and their chemistry and pharmacological applications have been extensively investigated. The more significant bioactivities of a variety of semicarbazones (antiprotozoa, and anticonvulsant) and thiosemicarbazones (antibacterial, antifungal, antitumoral, antiviral) and their metal comple-

xes have been reviewed together with the proposed mechanism of action and structure reactivity relationship (Pandeya et al., 1998; 2000; Mohamed et al., 2011). The title compounds were synthesized using the synthetic strategy described in Scheme 1.1-naphthylamine [i] treated with sodium cyanate in the presence of Glacial acetic acid gives urea of 1-naphthylamine [ii] .Compound [ii] treated in the presence of alkali and Hydrazine Hydrate gives urea of Semicarbazone [iii]. Compound [iv] was prepared by reaction of various aldeh-yde or ketone in the presence of Glacial acetic acid gives 1-naphthyl semicarbazone. Title compounds **AS-1** to **AS-11** were prepared by reaction of the appropriate aldehyde or ketone with compound [iv]. Accordingly and by considering the microbial potential of paraamino acetophenone semicarbazones derivatives were synthesized, spectroscopic analysis (include-ing IR and ^{1}HNMR), and evaluated for their antibacterial and antifungal activities.

Experimental

Materials and Methods

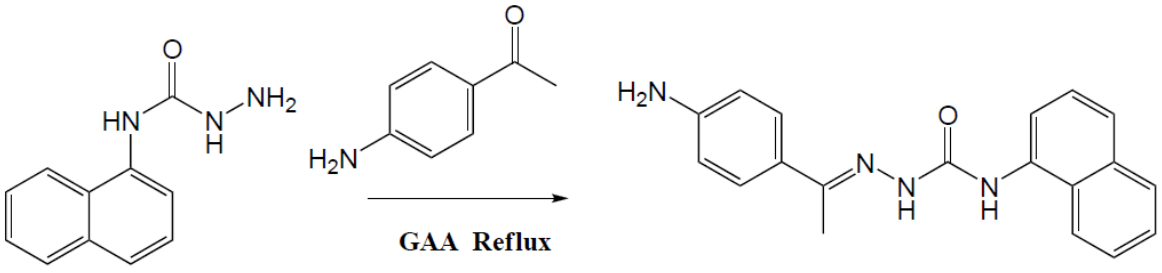
General method was used for the synthesis of the complexes. All chemical used were A.R. grade (USA). Solvents were doubly distilled, recrystal-lized/redistilled as necessary. All the chemicals and solvents used in this study were purchased from SD Fine and Hi-media (Mumbai). The reactions were monitored and checked on thin layer chromatography (TLC) precoated with silica gel G using solvent system benzene and methanol (9:3). Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on a Perkin Elmer IR spectrophotometer (KBr discs) (Perkin Elmer, Beaconsfield, UK). ^{1}H-NMR was recorded at 300 MHz spectra on a Bruker DRX-300 NMR spectrometer (DMSO-d6, TMS) (Bruker Bioscience, Billerica, MA, USA).

Synthesis of p-aminoacetophenone

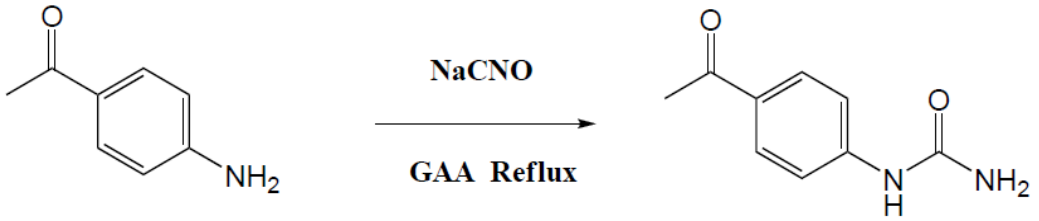
A mixture of urea p-aminoacetophenone, Sod. cynate, was refluxed in presence of Glacial acetic acid in Round Bottle Flask for about 4-5 hrs. Then the mixture was allowed to cool down. White curd like semi-solid formed. The product formed was filtered washed well with distilled water. Then this was left for drying.

Spectral data

p-aminosemicarbazide: Equimolar quantity of 1-naphthyl semicarbazide (1.1gm) (TS-1), p-aminoacetophenone (0.65gm) and GAA (10ml) was taken in Round Bottle Flask for 2-3



Scheme 1, Synthesis of p-aminoacetophenone semicarbazide



Scheme 2. Synthesis of p-aminoacetophenone

hrs. Then the mixture was cool down and evaporated on water bath, brown sticky solid obtained (AS-1). Yield: 47%, m.p.: ND, Rf : 0.77,IR (KBr cm-^{1}): 3219.3 (C-H str. Ar.), 1702.3 (C=O str.), 3468.3 (NH_2 str.), 1103.6 (C-N str.), ^{1}H-NMR (DMSO, δ, ppm, 300 MHz): 7.2-7.6 (m,4H,1-benzene-CH), 6.78-7.31 (m, 7H, 1-naph.-CH), 6.2 (s, 2H,-NH_2), 6.0 (s, 1H,-CONH), 5.3 (s, 1H, amide-NH).

*(4-Acetyl-phenyl) urea***:** p-amino acetophenone (5gm) was taken in beaker and dissolved in acetic acid (10ml). Sodium cynate (2.4gm) was taken in another beaker and dissolved in water (10ml). Now both solutions were mixed together then we obtained yellowish coloured liquid, now this was heated (simple heating) on waterbath for about 20-25 min., then allowed to stand for cooling , gradually brown crystal like solid appeared now this was filtered and dry (AS-2). Yield: 60.6 %, m.p.: 190-200 ^{o}C, Rf : 0.46, IR (KBr cm-^{1}): 3109 (C-H str. Ar.), 1690 (C=O str.), 2869 (CH_3 str.), 3455.3 (-NH_2 str.),^{1}H-NMR (DMSO,δ,ppm,300MHz): 7.75-8.84 (m,4H,1-benzene, CH), 6.4 (s, 2H, amide-NH_2), 6.0 (s, 1H, NH-urea), 2.55 (s, 3H, -CH_3)

{4-[1-(naphthalen-1-ylimino)-ethyl]-phenyl}-urea: A mixture of AS-2(2gm), 1-naphthylamine (2g) and GAA (10ml) was taken in Round Bottle Flask and refluxed for about 2 hrs. Then the mixture was cool down and filtered and washed with water, dry (AS-3). Yield: 47%, m.p.: 210 ^{o}C, Rf : 0.63,IR (KBr cm-^{1}): 3310.6 (C-H str. Ar.), 2906.1 (-CH_3 str.), 1690.6 (C=O str.), 3410.2 (-NH str.), ^{1}H-NMR (DMSO, δ, ppm, 300MHz): 7.21-7.30 (m, 4H, 1-benzene-CH), 6.55-7.31 (m, 7H, 1-naph.-CH), 6.4 (s, 1H, -C=O-NH_2), 6.0 (s, 1H, urea-NH) 1.73 (s, 3H, -CH_3)

4-(1-naphthalene semicarbazide ethyl) benzene-2-carbazide: A mixture of AS-2 (2gm), 1-naphthyl semicarbazide (2gm), GAA (10ml) was taken in Round Bottle Flask and refluxed for about 2.5 hrs. Then the reaction mixture was allowed to cool down and filtered by filter paper and dried (AS-4). Yield: 28.9%, m.p.: 220 ^{o}C, Rf : 0.57,IR (KBr cm-^{1}): 3309.6 (C-H str. Ar.), 2802.3 (-CH_3 str. Ali.), 1685.3 (C=O str.), 3465.2 (-NH str.), ^{1}H-NMR (DMSO, δ, ppm, 300MHz): 7.20-7.1 (m, 4H, 1-benzene-CH), 7.0 (s, 3H, amide-NH_2), 6.55-7.66 (m, 7H, 1-naph.-CH), 6.0 (s, 2H, urea-NH), 1.9 (s, 3H, -CH_3).

[4-(1-Hydrazono-ethyl)-phenyl]-urea: A mixture of AS-2 (2gm), Hydrazine-hydrate (10ml) and GAA (10ml) was taken in Round Bottle Flask and refluxed for about 3-4hrs. Then the mixture was evaporated on water bath in petri dish, yellow coloured power obtained (AS-5). Yield: 72%, m.p.: 180 ^{o}C, Rf : 0.5,IR (KBr cm-^{1}): 3196.5 (C-H str. Ar.), 2980.1 (CH3 str. Ali.), 1680.2 (C=O str.), 3436.1 (-NHstr.), ^{1}H-NMR (DMSO, δ ppm, 300 MHz): 7.1 (s,4H,amide-NH_2), 6.43-7.31 (m,4H,1-benzene-CH), 5.8 (s, 1H, -CH_3), 1.3 (s,3H,-CH_3)

4-(1-semicarbazide ethyl) benzene-1-carbazide: A mixture of AS-2(2gm), semicarbazide HCl (1.5g)[i], sodium acetate [CH3COONa] (1.5g) [ii] equimolar quantity taken of both [i,ii], methanol (10ml) was taken in Round Bottle Flask and refluxed for about 1-1.5 hrs. Then the mixture was allowed to cool down and filtered and washed with water, dried (AS-6).Yield: 48%, m.p.: 210 ^{o}C, Rf : 0.39,IR (KBr cm-^{1}): 3096.3 (C-H str. Ar.), 1700.3 (C=O str.), 2906.9 (CH3 str. Ali.), 3502.3 (-NH str.), ^{1}H-NMR (DMSO, δ, ppm, 300MHz):7.0 (s, 4H, amide-NH), 6.9-7.31 (m, 4H, 1-benzene-CH), 6.3 (s, 2H, urea-NH), 1.1 (s, 3H, -CH_3).

4-(1-thiosemicarbazide ethyl) benzene-1-carbazide: A mixture of AS-2(2gm), thiosemicarbazide (1.01g) and GAA (10ml) was taken in Round Bottle Flask and refluxed for about 2 hrs. Then the mixture was taken in petridish and washed with water and kept for evaporation, yellow sticky product was obtained washed it with acetone, sticky solid obtained [AS-7]. Yield: 10.11%, m.p.: ND, Rf : 0.76,IR (KBr cm-^{1}): 3100.3 (C-H str. Ar.), 3482.5 (-NH str.), 1070.6 (C-S str.), 1670.3 (C=O str.), 2970.6 (-CH_3 str. Ali.), ^{1}H-NMR (DMSO, δ, ppm, 300MHz): 7.6-7.7 (m,4H, 1-benzene-CH), 6.12 (s, 2H, urea-NH), 2.0 (s, 4H, amide-NH_2), 1.28 (s, 3H,-CH_3).

{4-(1-Phenyl-hydrazono) ethyl]-phenyl}-urea: A mixture of AS-2(2gm), Phenyl hydrazine (6ml) and GAA (10ml) was taken in Round Bottle Flask and refluxed for about 2 hrs. Then the mixture was evaporated on water bath, washed with DMF blackish sticky product obtained (AS-8). Yield: 50%, m.p.: ND, Rf : 0.56, IR (KBr cm-^{1}): 3105.6 (C-H str. Ar.), 2870.6 (-CH3 str. Ali.), 3410.6 (-NH str.), 1740.3 (C=O str.), ^{1}H-NMR (DMSO, δ, ppm,300MHz): 7.5-7.9 (m, 4H, benzylidimine-CH), 6.46-7.01 (m, 5H, 1-benzene-CH), 6.5 (s, 2H, amide-NH_2), 6.0 (s, 3H,-CH_3), 1.0 (s, 3H, urea-NH).

1-(4-Acetyl-phenyl)-3-(hydrazino-pyridin-4-yl-methylene)-urea: A mixture of AS-2(2gm), Isoniazid (1.4g) and GAA (10ml) was taken in Round Bottle Flask and refluxed for about 2-3 hrs. Then the mixture was taken on petridish and evaporated on water bath, then yellow sticky solid appeared (AS-9). Yield: 65%, m.p.: ND, Rf : 0.62, IR (KBr cm-^{1}): 3310.6(C-H str. Ar.), 3412.3(-NH str. Pyridine), 1685.3 (C=O str.), 2970.4 (CH_3 str. Ali.), ^{1}H-NMR (DMSO, δ, ppm, 300MHz): 8.02-8.83 (s, 4H, pyridine-CH), 7.75-7.84 (m, 4H, 1-benzene-CH), 2.8 (s, 2H, amide-NH_2), 2.55 (s, 3H, -CH_3), 2.0 (s, 1H, -NH).

[4-(3-Diethylamino-propionyl)-phenyl]-urea: A mixture of AS-2(2gm), Diethylamine (1ml), Formaldehyde (10ml), conc.HCl (1-2 drops), was taken in Round Bottle Flask and refluxed for about 1.5-2 hrs. Then the mixture was allowed to evaporated on water bath, after evaporation slightly heated on heating mental then yellowish power obtained AS-10].Yield: 80%, m.p.: 260 ^{o}C, Rf : 0.17,IR (KBr cm-^{1}): 3102.8 (C-H str. Ar.), 1605.3 (C=O str.), 3062.6 (-C_2H_5 str.), 3415.6 (-NH str.), ^{1}H-NMR (DMSO, δ, ppm, 300MHz) : 7.72-7.87 (m, 4H, 1-benzene-CH), 6.3 (s, 2H, amide-NH_2), 5.9 (s, 1H, urea-NH), 2.65 (s, 4H, -CH_2).

[4-(3-Piperidin-1-yl-propionyl)-phenyl urea: A mixture of AS-2(4.65gm), Piperidine (3ml), Formaldehyde (2.56ml), conc. HCl (1-2 drops) was taken in RBF and refluxed for about 1.5-2 hrs. Then the mixture was allowed to evaporate, yellow colour hygroscopic solid obtained (AS-11).Yield: 27%, m.p.: ND, Rf : 0.26, IR (KBrcm-^{1}):3205.6 (C-H str. Ar.), 1740.3 (C=O str.), 2840.2 (-CHstr.Pyridine), 3430.1 (-NHstr.), 3070.3(-CH_2str.), ^{1}HNMR (DMSO, δ, ppm,

300MHz):7.87-7.72 (m, 4H, 1-benzene-CH), 7.3 (s, 2H, amide-NH_2), 6.3 (s, 1H, urea-NH), 2.55-2.65 (s, 4H, -CH_2), 1.50-2.24 (m, 10H, Pipridine-CH_2).

Antimicrobial activity

Test microorganisms

A total of 4 clinically important bacterial strains viz. gram-positive *S. aureus* (ATCC 25323), *P.aeruginosa* (ATCC 27853) and gram-negative *E. coli* ATCC 25922, *E. faecalis* were selected in the investigation for antibacterial assay. Antifungal activities were evaluated on different strains of *candida* viz. *candida albicans* ATCC 90028, *Candida tropicalis* ATCC 750, and *Candida krusie* ATCC 6258. All micro-organism were cultured on their specified media i.e. Muller Hinton Agar (MHA, Hi-Media, Mumbai) and Sabouraud dextrose agar (SDA)/Potato dextrose agar (PDA) for bacterial and fungi culture respectively. All cultures strains were preserved at Department of Microbiology, Institute of Medical Sciences, BHU, Varanasi, India which were obtained from American Type Culture Collection (ATCC), MTCC and clinical strain. The fresh microbial broth cultures were prepared in normal saline before the screening procedure.

Antimicrobial activity

The paper disc diffusion method was used for antimicrobial assay (Gangwar *et al.,* 2012; Wiegand *et al.,* 2008) according to the guidelines of National Committee for Clinical Laboratory Standards (NCCLS, 2000). Briefly, 24/48 h old culture of selected microbes were adjusted to 0.5 MacFarland standard in sterile physiological saline to achive concentration of ~10^7 (colony forming units) CFU/ml. This bacterial/ fungal suspension was spread on the surface of MHA and SDA agar plates respectively (Bharti et al., 2010). The synthesized compounds impregnated with Whatman no. 1 filter paper disc (6 mm diameter) at a concentration of 20 µl/dics was placed on solidified media was allowed to diffuse for 5 min and the plates were kept for incubation at 37°C for 24 h for bacteria and 72 h at 25°C for fungal culture . Standard disc of antibiotics 6 mm in diameter were used as positive control. Dimethylsulfoxide (DMSO) was used as negative control. At the end of incubation, inhibition zones were examined around the disc which if present were measured with transparent ruler in millimeters. This study was performed in triplicate.

Determination of minimum inhibitory concentration (MIC)

It is defined as the lowest concentration of the compound which will inhibit the visible growth of microorganism in liquid media. MIC was determined by micro broth dilution method (Wiegand *et al.,* 2008; Gangwar *et al.,* 2011) using serially diluted (2 folds) according to the National Committee for Clinical Laboratory Standards (NCCLS) document M27-A. Specifically 0.1 ml of standardized inoculums of bacteria/fungus (1-2 × 10^7 CFU/ml) was added in each well of microtiter plate. Synthetic drugs concentrations were serially diluted in specific well and incubated aerobically at 37^{o}C for bacterial growth and 25ºC for fungal growth for 18-24 h. The lowest concentration (highest dilution) of the extract that produced no visible bacterial growth (no turbidity) when compared with the control were regarded as MIC.

Result and Discussion

Chemistry

Our synthetic route to target compounds AS-1 to AS-11 is presented in scheme 1. The para-ureidoacetophenone or 4-(Acetylphenyl)-urea (AS-2) react with various aldehyde and ketone to form required semicarbazones. The structures were characterized by spectral techniques. Physical characteristics and analytical data of the compounds were shown in table 1 and 2. In general, in IR spectra the carbonyl (C=O) peak of parent compound (semicarbazide) appears around 1685-1750 cm^{-1} where as amide (-$NHCONH_2$) peak showed the

Table 1. Physical characteristics of synthesized compounds

Compound	Mol. formula	Mol.wt.	Yield (%)	m.p (^oC)	Rf
AS-1	$C_{19}H_{18}N_4O$	318.37	54.5	ND	0.77
AS-2	$C_9H_{10}N_2O_2$	178.19	45.5	190-200	0.46
AS-3	$C_{19}H_{17}N_3O$	303.36	47	210	0.63
AS-4	$C_{22}H_{28}N_5O_2$	394.22	28.9	220	0.57
AS-5	$C_9H_{12}N_4O$	192.22	72	180	0.5
AS-6	$C_{11}H_{17}N_5O_2$	251.14	48	210	0.39
AS-7	$C_{13}H_{25}N_5O_2$	299.44	10	ND	0.76
AS-8	$C_{15}H_{16}N_4O$	268.31	50	ND	0.56
AS-9	$C_{15}H_{15}N_5O_2$	297.13	65	ND	0.62
AS-10	$C_{14}H_{21}N_3O_2$	363.34	80	260	0.17
AS-11	$C_{15}H_{21}N_3O_2$	275.35	27	ND	0.26

Table 2. Analytical data of synthesized compounds.

Compound	Solubility				Elemental Analysis (Calc./Found)		
	Benzene	Methanol	Water	DMSO	C	H	N
AS-1	is	is	is	s	71.68/ 71.18	5.70/ 5.20	17.60 /17.10
AS-2	ss	ss	ss	s	60.66/ 59.96	5.66/ 4.96	15.72 /15.02
AS-3	is	is	is	s	75.23/ 74.13	5.65/ 5.55	13.85 /13.75
AS-4	is	is	is	s	66.98/ 66.28	7.15/ 6.45	17.75/ 17.05
AS-5	is	is	is	s	56.24 55.74	6.29/ 5.79	29.15/ 28.75
AS-6	is	is	is	s	52.58 /52.28	6.82/ 6.52	27.87/ 27.57
AS-7	is	is	is	s	52.14 /51.84	8.42/ 8.12	23.39/ 22.09
AS-8	is	is	is	s	67.15/ 66.75	6.01/ 5.61	20.88/ 20.48
AS-9	is	is	is	s	60.60/ 61.56	5.09/ 5.15	23.56/ 22.63
AS-10	is	ss	is	s	63.85/ 63.45	8.04/ 7.64	15.96/ 15.56
AS-11	is	is	is	s	65.43/ 65.13	7.69/ 7.39	15.26/ 14.96

peak around 6.0 to 6.4 cm^{-1} , indicates the disappearance of carbonyl peak and thus confirms the synthesis of desired compounds. The 1H NMR of synthesized derivatives showed multiple signal corresponding to resonance of 1-naphthylamine protons at δ 1.69-1.73 ppm (-CH_3, methylene bridge), δ 6.44 to 7.31 ppm (1-naphthylylene-CH), δ 6.8 ppm (-CONH), in semicarbazide for N1 position. The results of elemental analysis were acceptable range, in comparison to theoretical value.

Antimicrobial activity

A series of para-amino acetophenone semicarbazones derivative prepared **(AS-1 to AS-11)** were tested *in-vitro* antibacterial against gram-positive and gram negative bacteria, antifungal against *candida* speices using two fold micro dilution method. The minimum inhibitory concentrations (MIC) values are presented in table 3 & 4. The result of antibacterial assay revealed that only three compounds i.e. **AS-3, AS-7 & AS-8** are active showing active zone of inhibitions in the range of 12.43 ± 0.30, 9.63 ± 0.23, 9.20 ± 0.79 against bacteria and 12.10 ± 0.62, 11.43 ± 0.25, 11.06 ± 0.70 and 10.90 ± 0.30 in mm. Compound AS-7 shows excellent activity against *E-coli* (MIC~ 50µg/ml) while **AS-3, AS-8** shows moderate against

Table 3. Antibacterial activity of synthesized compounds.

Sample	Gram Positive bacteria		Gram Negative bacteria	
	S. aureus	*P. aerogenosa*	*E. faecalis*	*E. coli*
AS-1	-	-	-	-
AS-2	-	-	-	-
AS-3	400	-	-	-
AS-4	-	-	-	-
AS-5	-	-	-	-
AS-6	-	-	-	-
AS-7	-			50
AS-8	-	200	200	
AS-9	-	-	-	-
AS-10	-	-	-	-
AS-11	-	-	-	-
Ciprofloxacine	3.12	6.25	3.12	6.25
DMSO	-	-	-	-

Table 4. Antifungal activity of synthesized compounds.

Sample	Pathogenic Fungi		
	Candida albicans	*Candida tropicalis*	*Candida krusie*
AS-1	-	-	-
AS-2	-	-	-
AS-3	100	100	50
AS-4	25		25
AS-5	50	25	-
AS-6	-	100	-
AS-7	-	-	-
AS-8	-	-	-
AS-9	50	-	-
AS-10	100	-	-
AS-11		-	-
Fluconazole	6.25	3.12	25
DMSO	-	-	-

S.aureus (MIC~ 400µg/ml) and *P.aeruginosa* (MIC~200 µg/ml). Antifungal activity revealed better inhibition compare to bacterial. Compound **AS-4** exhibit excellent inhibitition of *C.albicans* and *C.krusie* (MIC~ 25µg/ml) whereas compounds **AS-5, AS-6 & AS-9** exhibit moderate activity against *Candida* strains (MIC ~ 50, 100 µg/ml). The substit-ution with different substituent on the phenyl of the aldehydic and acetophenone group of the semicarbazones derivative plays an important role in the zone inhibition of bacteria/fungus.

In conclusion, a series of para-amino acetophenone semicarbazones derivative has been synthesized in appreciable yields. As far as the microbiological activities are concern, they were screened for *in-vitro* antimicrobial against bacteria and fungus, results are shown in table 3 and 4, it seems that the synthesized compounds exhibit variable effects and almost the same potency as standard drugs, thus shows substantial promise for the development of novel antimicrobial agents.

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Conflict of interest statement

There is no conflict of interest associated with the authors of this paper.

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