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Der Pharmacia Lettre, 2016, 8 (21):1-6
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Synthesis, Characterization and Antimicrobial Activity of Substituted Acetophenone Based Semicarbazones

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ABSTRACT

In the present study, a series of substituted Semicarbazones were synthesized, characterization and evaluated for their antimicrobial activity. A series of substituted semicarbazones were synthesized from substituted phenyl urea followed by hydrazine hydrate gave good yield of Semicarbazide, Which were further on treatment with appropriate substituted acetophenones yielded the semicarbazones (SC01-SC04). All the synthesized compounds were characterized on the basis of their IR, ^{1}H and ^{13}C NMR studies. The antimicrobial activity of all the compounds (SC01-SC04) showed significant activity against all the bacteria and fungus.

Key words: Semicarbazide, substituted acetophenones, antimicrobial.

INTRODUCTION

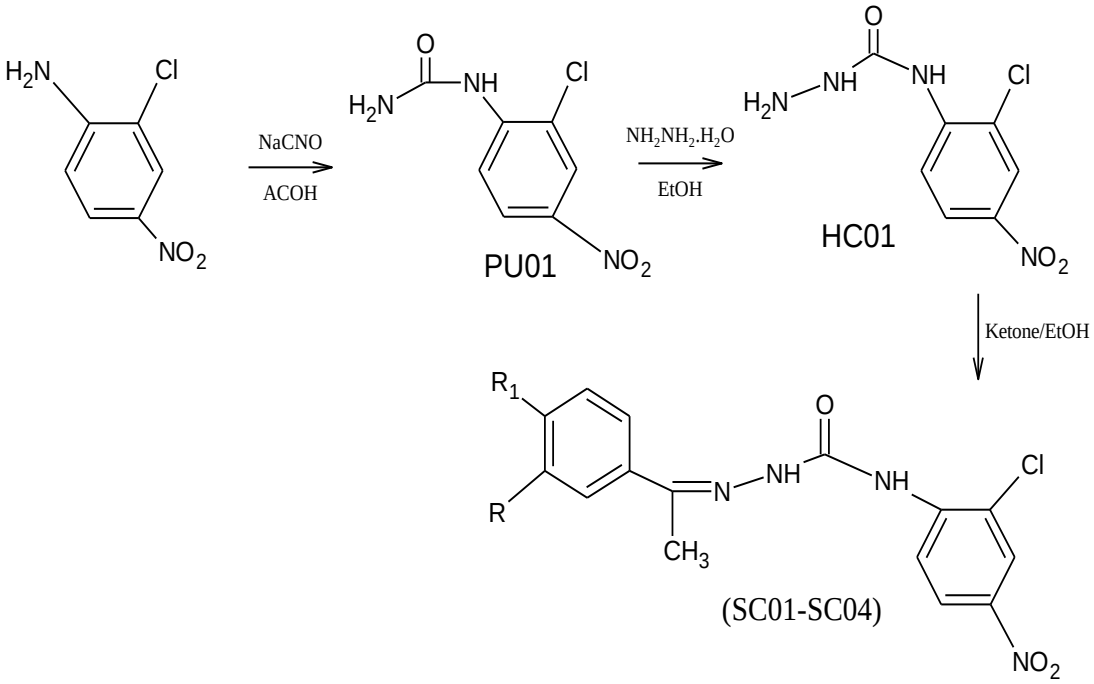
Semicarbazones are a class of compounds having the structure R2C=NNHC(=O)NH2 [1] formally derived by condensation of aldehydes or ketones with Semicarbazide [NH2NHC(=O)NH2] . They are classified as imine derivatives because they are formed from the reaction of an aldehydes or ketones with the terminal -NH2 group of Semicarbazide, which behaves very similarly to primary amines. The substituted semicarbazones possess various biological and pharmacological activities [2-13].

The Semicarbazide which are the raw material of semicarbazones have been known to have biological activity against many of the most common species of bacteria [14]. Semicarbazone, themselves are of much interest due to a wide spectrum of anti-fungal and anti-bacterial activities [15]. Recently some researcher had reviewed of bioactivity of semicarbazones and they have exhibited anticonvulsant [16], anti-tubercular [17], antioxidant [18], antimicrobial, analgesic, antipyretic [19] and anti-inflammatory activity [20].

Semicarbazones used as spectrophotometric agents as well for the analysis of metal ions [21] and are frequently used in the qualitative organic analysis of carbonyl compounds [22]. In view of these data we have undertaken the synthesis, characterization, and antimicrobial evaluation of substituted pyrazoles. All the synthesized compounds were characterized based on IR, 1H & 13C NMR spectral data and elemental analysis. The physical data of titled compounds are summarized and presented in the result and discussion part.

EXPERIMENTAL METHODS

The melting points were carried out in the open capillary tube and were uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate and spots were visualized by exposure to iodine vapour. IR spectra of compounds were scanned on Shimadzu IR spectrophotometer using KBr disc and expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-D_6 on BRUKER (400MHz) spectrometer using TMS as an internal standard (chemical shifts in δ, ppm). The elemental analysis for C, H, and N were in an agreement with the calculated values. The synthesis of the targeted compound was accomplished according to the reaction sequence illustrated in Scheme – 1.



SCO1 : R - H; R_1 - $CHMe_2$ SCO3 : R - H; R_1 - OCH_3

SCO2 : R = R_1 = CH_3 SCO4 : R = R_1 = OCH_3

Scheme-1

GENERAL PROCEDURE[23]

Synthesis of 1-(2-Chloro-4-nitrophenyl) urea (PU01)

The substituted aniline (8.628g, 0.05mole) was dissolved in glacial acetic acid (20mL) and diluted with water (100mL). To this, an equimolar quantity (3.25g, 0.05mole) of sodium cyanate in warm water (50mL) was added with constant (45minuts) stirring. The reaction-mixture could stand for 1 hr. and the solid precipitate formed was filtered off and dried after recrystallization from boiling water.

Synthesis of N-(2-chloro-4-nitrophenyl) hydrazine carboxamide (HC01)

To a solution of 1-(2-chloro-4-nitrophenyl) urea (PU01) (2.155g, 0.01mole) in ethanol (20 ml), an equimolar quantity of hydrazine hydrate (0.6g) was added. The reaction mixture was made alkaline by adding sodium hydroxide (1g). The reaction mixture was refluxed for 6 hrs and the precipitate obtained after cooling and filtered then washed and dried. Recrystallized from ethanol.

Synthesis of Substituted Semicarbazones (SC01-SC04)

A mixture of substituted Phenyl Semicarbazide (HC01) (0.01mole) and appropriate substituted acetophenones (0.01mole) in ethanol (25 mL) was refluxed, in the presence of few drops of glacial acetic acid. After 1 h, the precipitate obtained was filtered and recrystallized from ethanol.

RESULT AND DISCUSSION

Synthesis of substituted semicarbazone was obtained by the scheme –1. The required starting material Phenylsemicarbazide was synthesed from 1-(2-chloro-4-nitrophenyl)urea which on further treatment with substituted acetophenone yielded the substituted semicarbazone **(SC01-SC04)**. Compounds were characterized by IR, ^{1}H and ^{13}C NMR spectral data.

1-(2-Chloro-4-nitrophenyl) urea; (PU01)

m.p**:** 176^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3471 (NH str), 3093 (aromatic C-H str), 1635 (C=O str), 1566 (aromatic C=C), 1342 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 6.53 (s, 2H, $CONH_2$), 8.98 (s, 1H, Ar-NH), 6.5-8.6 (m, 3H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz)δ:168 (CONH), 145-117 (Ar-C)**;** Anal. Found: C, 39.06; H, 2.84; N, 19.45 (%). Calc. for ($C_7H_6ClN_3O_3$): C, 39.02; H, 2.81; N, 19.49 (%).

N-(2-Chloro-4-nitrophenyl) hydrazinecarboxamide; (HC01)

m.p**:** 198^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3471 (NH str), 3093 (aromatic C-H str), 1635 (C=O str), 1566 (aromatic C=C), 1365 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 4.53 (s, 2H), 8.17 (s, 1H, CONH), 8.19 (s, 1H, Ar-NH), 6.92 - 8.15 (m, 3H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 168 (CONH), 145-118 (Ar-C); Anal. Found: C, 36.48; H, 3.04; N, 24.32 (%). Calc. for ($C_7H_7ClN_4O_3$): C, 36.46; H, 3.06; N, 24.30 (%).

***N*-(2-Chloro-4-nitrophenyl)-2-(1-[4-(propan-2-yl) phenyl]ethylidene) hydrazine carboxamide; (SC01)**

m.p**:** 212^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3471 (NH str), 3093 (aromatic C-H str), 2924 (aliphatic C-H str), 1635 (C=O str), 1597 (C=N str), 1566 (aromatic C=C), 1342 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.16 (s,1H, CONH), 8.68-7.05 (m,7H, Ar - H), 6.64 (s,1H, Ar-NH), 2.98 (s,1H, C<u>H</u>-CH_3), 2.69 (s, 3H, CH_3), 1.28-1.26 (d, 6H CH-C<u>H</u>$_3$); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 185 (CONH), 154 (C=N), 145-112 (Ar – C), 34, 26, 23 (Ali-C); Anal. Found: C, 57.66; H, 5.13; N, 14.92 (%). Calc. for ($C_{18}H_{19}ClN_4O_3$): C, 57.68; H, 5.11; N, 14.95 (%).

***N*-(2-Chloro-4-nitrophenyl)-2-[1-(3,4-dimethylphenyl) ethylidene]hydrazine carboxamide; (SC02)**

m.p**:** 206^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3464 (NH str), 3060 (aromatic C-H str), 2924 (aliphatic C-H str), 1666 (C=O str), 1589 (C=N str), 1550 (aromatic C=C), 1342 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.18 (s, 1H,

CONH), 8.94-7.05 (m, 6H, Ar - H), 6.54 (s, 1H, Ar-NH) 3.89-3.87 (d, 6H, Ar-C$\underline{H}_3$), 2.71 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183 (CONH), 169 (C=N), 148-118 (Ar – C) 55, 26 (Ali-C); Anal. Found: C, 56.56; H, 4.76; N, 15.52 (%). Calc. for ($C_{17}H_{17}ClN_4O_3$): C, 56.59; H, 4.79; N, 15.53 (%).

***N*-(2-Chloro-4-nitrophenyl)-2-[1-(4-methoxyphenyl)ethylidene] hydrazinecarboxamide; (SC03)**

m.p**:** 215^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3471 (NH str), 3093 (aromatic C-H str), 2924 (aliphatic C-H str), 1635 (C=O str), 1566 (C=N str), 1504 (aromatic C=C), 1342 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.17, (s, 1H, CONH), 8.68-7.05 (m,7H, Ar - H), 6.64 (s,1H, Ar-NH), 3.86 (s,3H, OCH_3), 2.76 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183 (C=O), 167 (C=N) 149-118 (Ar – C), 27, 21(Ali-C); Anal. Found: C, 52.74; H, 4.16; N, 15.16 (%). Calc. for ($C_{16}H_{15}ClN_4O_4$): C, 52.77; H, 4.17; N, 15.14 (%).

***N*-(2-Chloro-4-nitrophenyl)-2-[1-(3,4-dimethoxyphenyl)ethylidene]hydrazine carboxamide; (SC04)**

m.p**:** 214^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3363 (NH str), 3062 (aromatic C-H str), 2924 (aliphatic C-H str), 1666 (C=O str), 1550 (C=N str), 1442 (aromatic C=C), 1327 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.13, (s, 1H, CONH), 8.68-6.64 (m,6H, Ar - H), 6.58 (s,1H, Ar-NH), 3.89-3.87 (d,6H, OCH_3), 2.71 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 184 (C=O), 164 (C=N) 159-111 (Ar – C), 56, 55, 26 (Ali-C); Anal. Found: C, 51.45; H, 4.34; N, 14.24 (%). Calc. for ($C_{17}H_{17}ClN_4O_5$): C, 51.48; H, 4.36; N, 14.26 (%).

ANTIMICROBIAL ACTIVITY

In vitro antibacterial activity was determined by Kirby-Bauer disc diffusion method against bacteria such as *Staphylococcus aureus* and *Bacillus* (Gram +ve), *Salmonella typhi* and *Pseudomonas aeruginosa* (Gram -ve) using *Ampicilin* as standard a standard drug. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 24 hrs incubation at 35-37^{0}C.

Similarly antifungal activity was performed against *Candida albicans*, flucanazole was used as standard drug. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 48 hrs at 25^{0}C.

The results of antibacterial and antifungal activity are presented in Table 1.

Zone of inhibition (mm) of synthesized compounds

All the synthesized compounds are showed significant activity against selected bacteria. Antifungal activity was performed on *Candida albicans.* The compounds of SC01 - SC04 was showed moderate activity against the fungus. The compound SC01 was more active among screened compounds.

Table-1. Antimicrobial activity of the synthesized compounds

Sample code	Anti-bacterial activity																Anti-fungal activity			
	Gram positive								Gram negative											
	Staphylococcus aureus				*Bacillus subtilis*				*Salmonella typhi*				*Pseudomonas aeruginosa*				*Candida albicans*			
	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std
SC 01	5	4	3	12	7	4	3	12	3	2	-	9	6	5	3	9	8	5	2	18
SC 02	5	4	2	10	9	5	-	13	4	2	-	5	9	8	6	10	6	5	3	18
SC 03	7	4	2	9	7	5	4	9	7	5	3	10	9	7	5	10	7	6	3	17
SC 04	9	7	5	13	10	6	4	14	6	4	3	10	8	6	4	10	8	6	4	20

CONCLUSION

In conclusion, the reaction profile explained in the present work is very efficient to synthesized substituted semicarbazones. The prepared compounds showed significant and moderate antimicrobial activities and these compounds will be taken for further pharmacological studies.

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