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NOVEL QUINOLINE THIOSEMICARBAZONE DERIVATIVES AS POTENTIAL ANTIMICROBIAL ACTIVITY

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ABSTRACT

The present study involves the synthesis of some novel N-aryl (2-chloro quinoline-3-carb aldehyde) thiosemicarbazone derivatives. The synthesis involves reaction between 2-chloro-3-formyl quinoline with various substituted aromatic thiosemicarbazides, in presence of catalytic amount of glacial acetic acid by refluxing in solvent ethanol. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR and Mass spectral analysis. Anti-microbial activity of the synthesized compounds was evaluated against various bacterial and fungal strains by determining their minimum inhibitory concentrations method. Some of the tested compounds exhibited significant anti-bacterial and anti-fungal activities.

Key Words: 2-chloro-quinoline-3-carbaldehyde, Thiosemicarbazones, Anti-microbial and anti-fungal activities.

INTRODUCTION

Many naturally occurring and synthetic compounds bearing quinoline scaffold possess interesting biological properties like Anti-malarial (Vlabhov R *et al*., 1990), Antimicrobial (Pramod N *et al*., 2011), Antioxidant (Patel Ashish Haribhai *et al*., 2011), Wound healing (Jayakumar BHM *et al.*, 2012), Anti-neoplastic (Catoen-Chackal S *et al.*, 2004), Anti-leishmanial (Sahu NP *et al*., 2005), Anticonvulsant (Zie Z *et al*., 2005) and quinoline and its derivatives possess many other biological and pharmacological activities. Substituted thiose micarbazides: A versatile molecule for the synthesis of thiadiazole, imidazolinones and thiosemicarbazones possessing multiple biological, anti-tubercular, anti-cancer, anti-viral, anti-amoebic, herbicidal and anti-microbial activities. Thiosemicarbazides derivatives are associated with diverse biological activities. Probably by virtue of toxophoric -N-C=S grouping. The advent of sulfa drugs and the later discovery of mesoionic compounds greatly accelerated the rate of progress in the field of thiadiazoles; imidazolinones and substituted quinolines have attracted considerable attention also possesses significant biological and pharmacological properties (Leon Katz *et al*., 1951; Wiles DM *et al*., 1968). Therefore, in this work we have endeavored to explore some new novel 2-chloro-3-formyl quinoline thiosemicarbazone heterocycles for their possible biological and pharmacological properties. thiosemicarbazides, as a part of the present investigations. Thus, it has been considered interesting to bring together the quinoline system with thiosemicarbazide to obtain quinoline thiosemicarbazones and to evaluate them for their possible biological and pharmacological activities.

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MATERIALS AND METHODS

All chemicals used were of analytical grade and

purchased from SD Fine. Melting points of all the synthesized compounds were determined by open capillary tube method. The purity of all compounds was checked by TLC technique and spots were visualized using UV radiation/iodine chamber. IR spectra were recorded on IR spectrophotometer by using KBr pellets technique.[1]H-NMR was recorded on DRX-300 MHz FT spectrophotometer by using DMSO as solvent and TMS as internal standard. The chemical shift was expressed in δ ppm.

Synthesis of 2-chloro-3-formyl quinoline (1)

The synthesis of 2-chloro-3-formyl-quinoline is based on review of literature (Pramod N, Jayakumar swamy *et al.,* 2011; Ambika srivastava *et al.,* 2005).

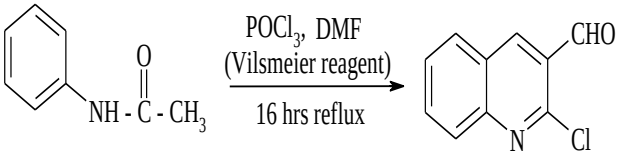
Synthesis of 4-aryl substituted thiosemicarbazide (2)
General procedure

Freshly distilled aniline (0.1 mol) was dissolved in ammonia solution (20ml d=0.88) and carbon disulphide 8 ml was added to it gradually with stirring in ice bath ethanol (30 ml) was added and stirring was continued until carbon disulphide completely dissolved. The reaction mixture was allowed to stand for 2-3 hour. An aqueous sodium chloroacetate (0.1 m) solution was added followed by hydrazine hydrate (10ml, 50%). The reaction mixture was stirred for 2-3 hours and allowed to stand over night. The crystal separated were filtered and recrystalized from ethanol. Same method was followed for other substituted thiosemicarbazide using different substituted anilines yield 70-75%.

Synthesis of N-aryl (2-chloro quinoline-3-carbaldehyde) thiosemicarbazone (3a-o)
General Procedure: Scheme-1

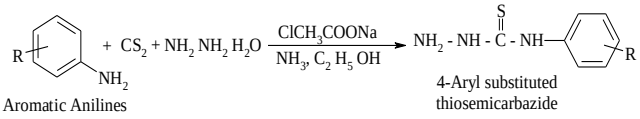
The 2-chloro-3-formyl quinoline compound (0.1m) was heated with a solution of the 4-aryl substituted thiosemicarbazide (0.1 m) in ethanol or methanol 200-400 ml containing a few drops of glacial acetic acid the mixture was refluxed for 2-3 hours and then concentrated to 100 ml. The crude product was purified by recrystalisation from aqueous DMF to get a pure crystalline compound. Adopting the similar procedure fifteen 2-chloro quinoline-3-carbaldehyde-N-aryl thiosemicarbazones were synthesized whose physical and analytical property's particulars are given in Table 1.

The required 2-chloro-3-formyl quinoline are prepared by adopting standard procedure[10,13-14] from N-aryl acetamides as follows: The vilsmeier approach, involving the reaction of N-aryl acetamides with vilsmeier reagent yielded 2-chloro-3-formyl quinoline, in good yield and identified by comparing their physical constants and elemental analyses.



Acetanilide 2-Cl, 3-CHO Quinoline **(1)**

Similarly, different aryl thiosemicarbazide have been obtained from the starting compound aryl amines on reaction with carbon disulphide and ammonia with ethanol and sodium chloroacetate followed by the addition of hydrazine hydrate yielded aryl-thiosemicarbazide and identified by their literature melting point.



(2)

Reaction of aryl thiosemicarbazide with 2-chloro-3-formyl quinoline (3a-o)

The possibility for the given aldehyde to undergo its characteristic nucleophilic addition followed by the elimination of a water molecule to yield a Schiff's base. Then, the 2-chloro-3-formyl quinoline has been condensed with as many as fifteen different aryl thiosemicarbazide by heating under reflux on water bath, an equimolar mixture in ethanol containing a trace of glacial acetic acid. The resultant products have been purified by recrystalisation in DMF and characterized as the respective N-aryl-(2-chloro quinoline-3-carbaldehyde) thiosemicarbazone.

For instance, 2-chloro-3-formyl quinoline **(1)**, has been condensed by heating under reflux on water bath with N - (p-methyl phenyl) thiosemicarbazide **(2)** in ethanol containing few drops glacial acetic acid. TLC monitoring of the reaction has clearly indicated the formation of single product. The product on purification by recrystalisation from dimethyl formamide has yielded an yellow colour crystalline compound M.P. 196^{0}C.

Spectral data

2-chloroquinoline-3-carbaldehyde-N-phenyl thiosemicarbazone(3a). Yield 85%, mp. 198^{0}C, IR (KBr) cm-^{1}: 3360(NH), 3120(Ar-NH), 1605(C=N), 1530(C=C), 1200(C=S), 920(N-N), 710 (C-Cl), ^{1}HNMR (CDCl3, DMSO-d6):7.20-8.24 (m, 10H, Ar-H), 9.22 (s, 1H, -NH-C=S), 10.12 (s, 1H, Ar-NH), 8.72 (s, 1H, CH=N-).

2-chloroquinoline-3-carbaldehyde-N-(4-Methylphenyl) thiosemicarbazone (3h). Yield 86%, mp. 196^{0}C, IR (KBr)

cm-^{1}: 3330(NH), 3220(Ar-NH), 1600(C=N), 1530(C=C), 1190(C=S), 930(N-N), 730(C-Cl), ^{1}HNMR (CDCl3, DMSO-d6):2.30 (s, 3H, -C<u>H</u>$_3$), 7.05 - 8.40 (m, 9H, Ar-<u>H</u>), 9.20 (s, 1H, -N<u>H</u>-C=S), 10.00 (s, 1H, Ar-N<u>H</u>) , 8.80 (s, 1H, -C<u>H</u>=N). MS : M/Z 355 (M^+), 357 (M+2).

2-chloroquinoline-3-carbaldehyde-N-(4-Methoxyphenyl) thiosemicarbazone(3k). Yield 63%
mp. 198^{0}C, IR (KBr) cm-^{1}: 3400(NH), 3100(Ar-NH**),** 1610(**C=N),** 1570(**C=C),** 1200(**C=S),** 940(**N-N),** 720(**C-Cl),** ^{1}HNMR (CDCl3, DMSO-d6):3.90 (s, 3H, -0C<u>H</u>$_3$), 6.9-8.4 (m, 9H, Ar-<u>H</u>),8.4 (s, 1H, -N<u>H</u>-C=S), 10.00 (s, 1H, Ar-N<u>H</u>), 8.80 (s, 1H, C<u>H</u>=N-). MS: M/Z 370 (M^+), 372 (M+2).

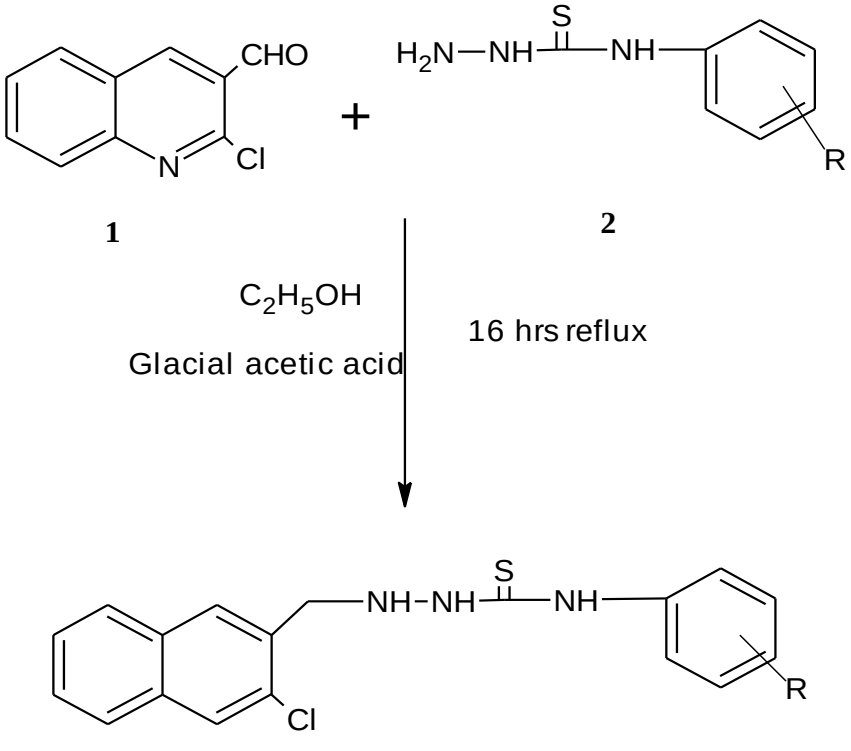
2-chloroquinoline-3-carbaldehyde-N-(4-Flurophenyl) thiosemicarbazone(3l). Yield 84%, mp. 192^{0}C, IR (KBr) cm-^{1}: 3360(NH), 3120(Ar-NH), 1605(C=N), 1558(C=C), 1158(C=S), 960(N-N), 710(C-Cl), ^{1}HNMR (CDCl3, DMSO-d6): 7.10-8.34 (m, 9H, Ar-H), 9.20 (t, 1H, -NH-C=S), 9.94 (s, 1H, Ar-NH), 8.85 (d, 1H, CH=N-). MS: M/Z 358 (M^+), 360 (M+2).

2-chloroquinoline-3-carbaldehyde-N-(4-Bromophenyl) thiosemicarbazone(3n). Yield 76%, mp. 198 ^{0}C, IR (KBr) cm-^{1}: 3310(NH), 3160(Ar-NH**),** 1610(**C=N),** 1535(**C=C),** 1075(**C=S),** 958(**N-N),** 724(**C-Cl),** ^{1}HNMR (CDCl3, DMSO-d6): 7.20-8.18 (m, 9H, Ar-<u>H</u>), 9.36 (s, 1H, -N<u>H</u>-C=S), 10.12 (s, 1H, Ar-N<u>H</u>), 8.53 (s , 1H, C<u>H</u>=N-).

ANTI-MICROBIAL ACTIVITY

All synthesized compounds were screened for In vitro antibacterial activity against two strains of microorganisms namely *Staphylococcus aureus (Gram+ve) and Escherichia coli (Gram-ve)* by MIC (Streak plate method). All those compounds screened for antibacterial activity were also tested for their antifungal activity by using cup plate method. The fungi employed for screening were: *Aspergillus flavus* and *Candida albicans*. Known antibiotics like procaine penicillin and griseofulvin were used for comparison purpose respectively.

Scheme-1



1 **2**

3(a-o)

R = H, 2 -NO_2, 3 -NO_2, 4 -NO_2, 2 -Cl, 3 -Cl, 4 -Cl, 2 -OCH_3, 3 -OCH_3, 4 -OCH_3, 2 -CH_3, 4 -CH_3, 3,4 -Cl_2 and 4 - F, 4 –Br, 2,4 – (CH_3)$_2$.

Table 1. Characteristic analytical data of N-aryl (2-chloro quinoline-3-carbaldehyde) thiosemicarbazones

Compd. Code	R	Mol. Formula	Mol.wt	Melting point	% Yield
3a	H	$C_{17}H_{13}N_4SCl$	340.8	198	85
3b	2-Cl	$C_{17}H_{12}N_4SCl_2$	375.2	218	72
3c	3-Cl	$C_{17}H_{12}N_4SCl_2$	375.2	182	68
3d	4-Cl	$C_{17}H_{12}N_4SCl_2$	375.2	298	53
3e	3-NO2	$C_{17}H_{12}N_5O_2SCl$	385.8	266	74
3f	4-NO2	$C_{17}H_{12}N_5O_2SCl$	385.8	328	57
3g	2-CH3	$C_{18}H_{15}N_4SCl$	354.8	168	73
3h	4-CH3	$C_{18}H_{15}N_4SCl$	354.8	196	86
3i	2-OCH3	$C_{18}H_{15}N_4OSCl$	370.8	218	72
3j	3-OCH3	$C_{18}H_{15}N_4OSCl$	370.8	212	75
3k	4-OCH3	$C_{18}H_{15}N_4OSCl$	370.8	198	63
3l	4-F	$C_{17}H_{12}N_4SFCl$	358.8	192	84
3m	3,4-Cl	$C_{17}H_{11}N_4SCl_3$	409.7	286	52
3n	4-Br	$C_{17}H_{12}N_4SBrCl$	419.7	198	76
3o	2,4-CH3	$C_{19}H_{17}N_4SCl$	368.8	236	87

Table 2. *In vitro* antimicrobial screening data of 3a-o (MIC in µg/ml)

Compound code	Staphylococus aureus (G^{+ve})	Escherichia coil (G^{-ve})
Procaine Penicillin (Std.)	31.25	62.5
3a	62.5	125
3b	250	500
3c	250	250
3d	125	125
3e	62.5	250
3f	125	125
3g	125	500
3h	62.5	125
3i	125	250
3j	62.5	125
3k	62.5	125
3l	125	250
3m	62.5	125
3n	125	250
3o	62.5	125

Table 3. *In vitro* antifungal screening data of 3a-o (MIC in µg/ml)

Name of compound	Mean zone of inhibition in (mm)			
	Candida albicans		*Aspergillus flavus*	
	50µ	100µ	50µ	100µ
Griseofulvin (Std.)	17	23	16	24
3a	13 (0.76)	17 (0.74)	12 (0.75)	16 (0.66)
3b	16 (0.94)	19 (0.82)	14 (0.87)	19 (0.79)
3c	16 (0.94)	21 (0.91)	11 (0.68)	21 (0.87)
3d	12 (0.70)	18 (0.78)	13 (0.81)	20 (0.83)
3e	14 (0.82)	16 (0.69)	14 (0.87)	21 (0.87)
3f	15 (0.88)	17 (0.74)	11 (0.68)	18 (0.75)
3g	13 (0.76)	18 (0.78)	13 (0.81)	18 (0.75)
3h	13 (0.76)	16 (0.69)	12 (0.75)	17 (0.70)

3i	12 (0.70	16 (0.69)	14 (0.87)	20 (0.83)
3j	16 (0.94)	20 (0.87)	13 (0.81)	18 (0.75)
3k	14 (0.82)	17 (0.74)	12 (0.75)	17 (0.70)
3l	13 (0.76)	16 (0.69)	13 (0.81)	19 (0.79)
3m	16 (0.94)	19 (0.82)	14 (0.87)	21 (0.87)
3n	12 (0.70)	17 (0.74)	12 (0.75)	16 (0.66)
3o	13 (0.76)	16 (0.69)	13 (0.81)	19 (0.79)

Std: Griseofulvin (Grisovin FP); Mean zone of inhibition is including bore diameter; Bore diameter is 8 mm;
Activity index = Test compound/Standard compound

DISCUSSION

Antibacterial activity

We can conclude that the test compound namely 3 - a, h, j, k, m and o were found to be having more potent antibacterial activity. This was evident by observing the MIC at 62.5 µg/ml and 125 µg/ml against S. aureus (G+ve) and E. coli (G-ve) respectively. The MIC of the above said compounds was seems to be only one fold increases in MIC of the reference standard drug (31.25 µg/ml and 62.5 µg/ml respectively against S. aureus and E. coli). However, the compounds 3-d and f, were found to be more potential antibacterial agents against G-ve organism namely E. coli. this was evidenced due to their observed MIC at 125 µg/ml. were as rest of the screened synthesized compound were exhibited mild to moderate antibacterial activity against tested organism.

Antifungal activity

The results of antifungal activity summarized in Table-3 reveals that compounds 3 - b, c, j and m were exhibited activity near to that of standard at 50 µg/ml and compounds 3-c & j showed equipotent activity compare to that of standard at 100 µg/ml against *Candida albicans*. However, the rest of the compounds showed mild to moderate activity. The compounds 3 - b, e, i and m exhibited activity closer to standard against Aspergillus flavus at 50 µg/ml concentration. The remaining Compounds have shown mild to moderate activity. Whereas the compounds 3 - c, e and m exhibited antifungal activity closer to that of standard at 100 µg/ml. However, the rest of the compounds showed mild to moderate activity.

CONCLUSION

Fifteen new compounds of 2-chloroquinoline-3-carbaldehyde-N-aryl thiosemicarbazones were synthesized. All synthesized compounds were characterized by TLC, IR and some selected compounds were characterized by 1H-NMR and MASS spectral properties. All synthesized compounds were screened for antibacterial and antifungal activities. Tested compounds exhibited good to moderate antibacterial activity against both gram positive S. aureus and gram negative E. coli. Few of the new compounds exhibited antifungal activity equal to standard drug against Aspergillus flavus and *Candida albicans*.

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