Jayakumar Swamy BHM. *et al.* / *International Journal of Phytopharmacology.* 3(2), 2012, 157-162.

e- ISSN 0975 – 9328
Print ISSN 2229 – 7472

International Journal of Phytopharmacology

Journal homepage: www.onlineijp.com

IJP

THIADIAZOLE-QUINOLINE DERIVATIVES AS POTENTIAL WOUND HEALING ACTIVITY

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ABSTRACT

Ten substituted N-aryl-5-phenyl 1,3,4-thiadiazoles (III) were synthesized by the reaction of different substituted chloro-quinolines (IIa) and hydroxy-quinolines (IIb) with 2-amino-5-phenyl 1,3,4-thiadiazole (I) in the presence of glacial acetic acid in refluxing ethanol. The newly synthesized compounds were characterized by spectroscopic methods. Further, the synthesized few selected compounds were screened wound healing activity by standard method. Results of the activities reveal that, some compounds exhibited moderate to good selected compounds showed wound healing activity.

Key Words:- Thiosemicarbazide, Thiosemicarbazone, 2-Amino 5-Phenyl 1, 3, 4-Thiadiazole, Wound healing activity.

INTRODUCTION

Nitrogen containing heterocycles are one of the most extensively synthesized and screened compounds as they show diverse pharmacological activities. Thiadiazole nucleus constitutes the active part of several biologically active compounds, including antimicrobial (Jumat Salimon *et al*., 2010; Varsha Jatav *et al*., 2006; Khosrow Zamani *et al*., 2004), diuretics (Sanmati K Jam *et al*., 2004), antioxidant (Venkatapuram Padmavathi *et al*., 2009) and Muscle relaxant (Ali Almasirad *et al*., 2007) activities. Thiadiazole and quinoline compounds constitute one of the major classes of nitrogen containing heterocycles. These possess different pharmacological activities and hence, attracted the attention of many scientists as the novel candidates for anti-microbial, anti-inflammatory, anti-cancer, and anti-oxidant activities.

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The anti-malarial activity of Quinoline derivatives is well known from many years .The various derivatives of quinolines are used to treat malaria (Vlabhov R *et al*., 1990). Furthermore quinoline compounds can possess anti-bacterial (Natesh Rameshkumar *et al*., 2003; Pramod N *et al*., 2011), anti-fungal (Monika Gupta *et al*., 2010) anti-viral (Pandey V K *et al*., 2001) antituberculotic (Vijay K Agrawal *et al*., 1999) etc. The utility of quinoline derivatives in the preparation of some dyes and pigments has been reported. It has been observed that chloroformyl quinoline compounds possess biological and pharmacological activity due to the presence of -Cl and -CHO at the appropriate position of the ring.

The advent of sulfa drugs and the later discovery of mesoionic compounds greatly accelerated the rate of progress in the field of thiadiazoles and substituted quinolines. These have attracted considerable attention, as these agents possess significant biological and

pharmacological properties. Therefore, in this work we have endeavored to explore some new novel thiadiazole-quinoline heterocycles for their possible biological and pharmacological properties.

MATERIALS AND METHODS

All chemicals used were of analytical grade from, SD Fine. Melting points of all the synthesized compounds were determined by open capillary tube method. These are uncorrected. The purity of all compounds was checked by TLC was run on Silica Gel G plates using Chloroform and ethyl alcohol (8:2). Spots were visualized using iodine vapour chamber. IR spectra were recorded on Shimadzu IR spectrophotometer by using KBr pellets technique. ^{1}H-NMR was recorded on Bruker AMX 60 MHz spectrophotometer by using DMSO as solvent.

Methods

Synthesis of 2-amino-5-phenyl 1, 3, 4-thiadiazole (I)

Synthesis of 2-amino-5-phenyl 1,3,4-thiadiazole (3a) was achieved using a modification of the original procedure of Ranga Rao and Srinivasan.

Step-1: Synthesis of Thiosemicarbazone

Aromatic aldehyde in warm alcohol (300 ml) was added to a solution of thiosemicarbazide (0.2 mol) in hot water (300 ml) slowly with continuous stirring. The products, which separated, were filtered off and recrystalized from 50% aqueous ethanol, yield 92%, mp: 158-160°c.

Step-2: Synthesis of 2-amino-5-phenyl 1, 3, 4-thiadiazole

Thiosemicarbazone (0.05 mol) was suspended in 300 ml distilled water in a 1000 ml beaker. Ferric chloride (0.15 mol) in 300 ml distilled water was added to it. The contents were refluxed for 6 hrs at 80-90°. Then it was filtered hot. A mixture of citric acid (0.11 mol) and sodium citrate (0.05 mol) was added to the solution and stirred. After cooling, the whole solution was taken in a bigger vessel (to account for the increase in volume) and neutralized with 10% aqueous ammonia. The precipitate that separated out was filtered and recrystalized from 25% aqueous ethanol, yield 50-52%, mp: 222-224°c.

Synthesis of substituted chloro-quinolines (Ambika Srivastava *et al*., 2007) **(II-a)**

Dimethyl formamide (9.13 gm, 0.125m) was cooled to 0°c in a flask equipped with a drying tube and phosphorus oxychloride (53.7 gm, 32.2ml) was added drop wise with stirring to this solution N-aryl acetamides (0.05M) was added and after 5 min the solution was kept under reflux for 16 hrs. The reaction mixture was poured in to ice water (300 ml) and stirred for 30 min at 0-10°c. When substituted chloro quinolines separated as yellow precipitate, it was filtered, washed with water. It was recrystalized from ethyl acetate into yellow needles M.P. 180-238°c, yield 5.5 gm.

Synthesis of substituted hydroxy-quinolines (II-b)

A mixture of chloroquinolines (0.01 M) and aqueous hydrochloric acid (35 ml; 4 M) was heated under reflux for 4 hrs and then allowed to cool at room temperature. The mixture was poured on to crushed ice. When hydroxy quinolines separated as yellow solid, it was filtered, washed and dried. It was recrystalized from aqueous acetic acid in to yellow sticky needles, M.P. 248-310°c, yield 1.60 gm.

Synthesis of substituted N-aryl-5-phenyl 1, 3, 4-thiadiazoles (III)

General Procedure

The solution of 2-amino-5-phenyl 1, 3, 4-thiadiazole (0.01mol) in ethanol (100-120 ml) was heated with the solution of different substituted chloro and hydroxyl-quinolines (0.01mol) in glacial acetic acid (80-100 ml) and refluxed for 37-50 hours. The crude product was purified by recrystalisation from ethanol/glacial acetic acid respectively, to get pure crystalline compounds.

Adopting the similar procedure ten N-aryl-5-phenyl 1,3,4-thiadiazoles were synthesized whose physical and analytical property's particulars are given in Table-1.

Spectral data

I. ASH-2: IR (KBr) cm-1: 2914 (C-H), 1656 (C=N), 1567 (C=C), 845 (N-N), 688 (C-S). 1HNMR (DMSO) δ ppm: 2.224 (s, 3H, CH3), 7.16-7.95 (m, 9H, Ar-H), 10.265 (s, 1H,-N=CH-), ESIMS (m/z): 365 (M+).

II. ASH-7: IR (KBr) cm-1: 3176 (N-H), 3040 (C-H), 1669 (C=O), 1611 (C=N), 1564 (C=C),
849 (N-N), 640 (C-S), 1H NMR (DMSO) δ ppm: 2.451 (s, 3H, CH3), 7.16-7.78 (m, 9H, Ar-H), 8.497 (s, 1H, N-H), 10.263 (s, 1H,-N=CH-), ESIMS (m/z): 346 (M+).

III ASH-8: IR (KBr) cm-1: 3140 (N-H), 2979 (C-H), 1662 (C=O), 1624 (C=N), 1560 (C=C),
898 (N-N), 601 (C-S), H NMR (DMSO) δ ppm: 2.348 (s, 3H, CH3), 7.26-7.69 (m, 9H, Ar-H), 8.416 (s, 1H, N-H), 10.236 (s, 1H,-N=CH-), ESIMS (m/z): 346 (M+).

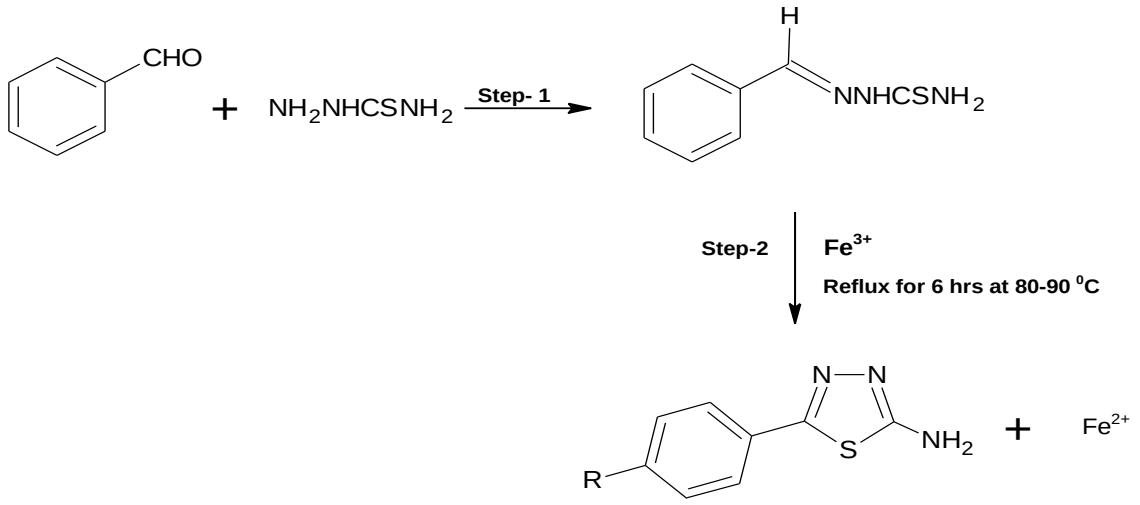
IV. ASH-9: IR (KBr) cm-1: 3139 (N-H), 2983 (C-H), 1678 (C=O), 1613 (C=N), 1550 (C=C), 895 (N-N), 666 (C-S), 1H NMR (DMSO) δ ppm: 7.35-8.06 (m, 9H, Ar-H), 8.487 (s, 1H, N-H), 10.232 (s, 1H,-N=CH-), ESIMS (m/z): 366 (M+).

V. ASH-10: IR (KBr) cm-1: 3176 (N-H), 3040 (C-H), 1669 (C=O), 1611 (C=N), 1564 (C=C), 849 (N-N), 640 (C-S), 1H NMR (DMSO) δ ppm: 2.411 (s, 3H, CH3), 7.09-7.81 (m, 9H, Ar-H), 8.462 (s, 1H, N-H), 10.219 (s, 1H,-N=CH-), ESIMS (m/z): 346 (M+).

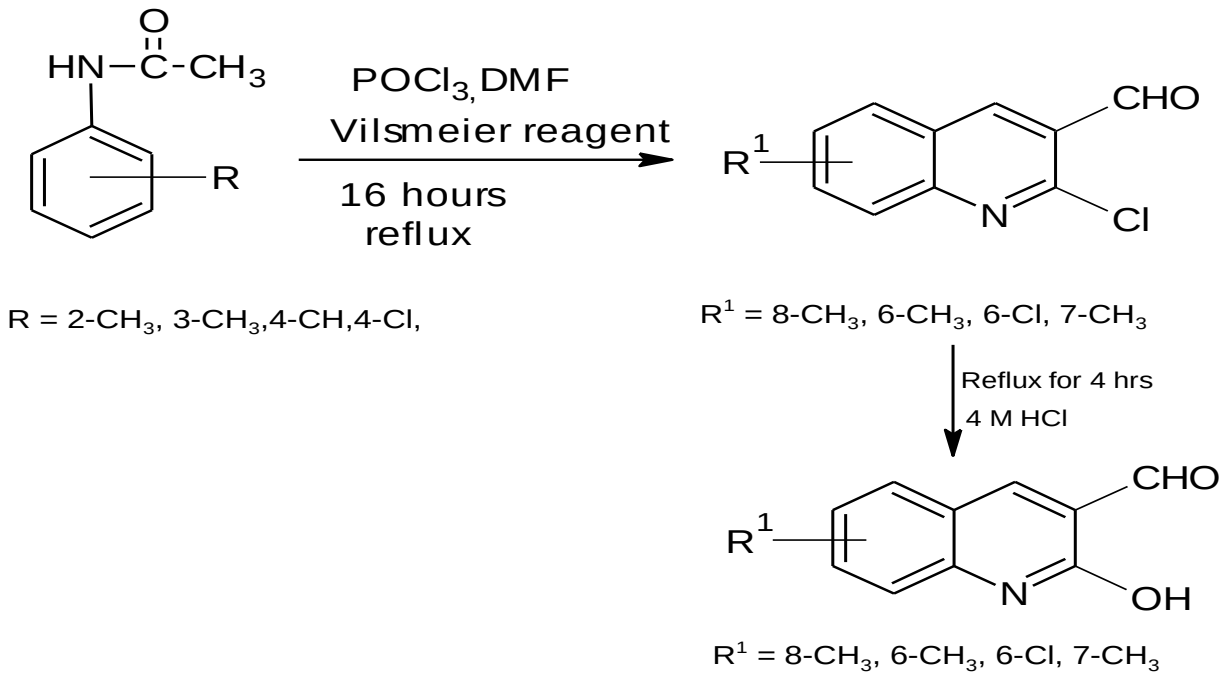
WOUND HEALING ACTIVITY

Wound healing activity was performed by excision wound model according to references (Karodi R *et al*., 2009; Ayyanar M *et al*., 2009).

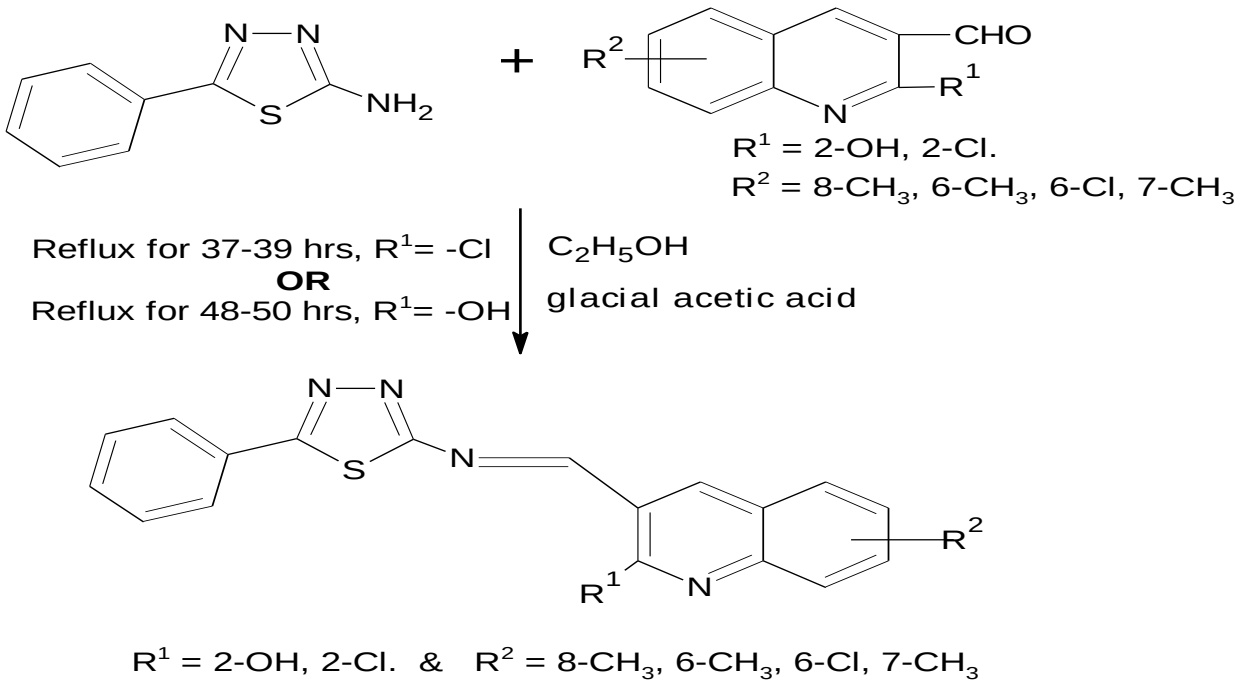
Synthesis of 2-amino-5-phenyl 1, 3, 4-thiadiazole (I)



Synthesis of substituted chloro-quinolines



Scheme-I:



SCHEME- I

Fig 1. N-aryl-5-phenyl 1,3,4-thiadiazoles

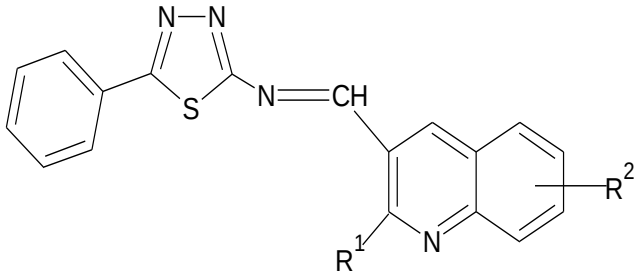


Table 1. Characteristic analytical data of substituted N-aryl-5-phenyl 1,3,4-thiadiazoles

S. No	Compounds Code	M.P °c	% Yield	Mol. Formula	Mol. Wt.	Calculated %		
						C	H	N
1	ASH-1	236-238	59	$C_{18}H_{11}N_4SCl$	351	61.62	3.16	15.97
2	ASH-2	220-224	60	$C_{19}H_{13}N_4SCl$	365	62.55	3.59	15.36
3	ASH-3	196-198	58	$C_{19}H_{13}N_4SCl$	365	62.55	3.59	15.36
4	ASH-4	234-238	56	$C_{18}H_{10}N_4SCl_2$	385	56.11	2.62	14.54
5	ASH-5	180-182	62	$C_{19}H_{13}N_4SCl$	365	62.55	3.59	15.36
6	ASH-6	248-252	86	$C_{18}H_{12}N_4OS$	332	65.04	3.64	16.86
7	ASH-7	260-262	59	$C_{19}H_{14}N_4OS$	346	65.88	4.07	16.17
8	ASH-8	270-274	66	$C_{19}H_{14}N_4OS$	346	65.88	4.07	16.17
9	ASH-9	308-310	62	$C_{18}H_{11}N_4OSCl$	367	58.94	3.02	15.27
10	ASH-10	272-276	63	$C_{19}H_{14}N_4OS$	346	65.88	4.07	16.17

RESULTS

Table 2. Effect of topical application of 2.5% w/w ointment of synthesized compounds on excision (open) wound model

Groups	% Contraction of wound on different days			(sq.mm)	Epithelization time in days
	4th day	8th day	12th day	16th day	
Control	20.14 ± 0.48	37.81 ± 1.18	61.08 ± 0.09	71.55 ± 0.29	24.5 ± 0.50
Povidine iodine	36.59 ± 1.11***	61.84 ± 3.41***	84.3 ± 4.05***	98.25 ± 0.13***	18.0± 0.00***
ASH- 2	24.62 ± 2.40**	53.23 ± 0.98**	77.2 ± 0.92**	87.42 ± 0.85**	21.5 ± 0.50**
ASH- 5	26.71 ± 0.56**	54.53 ± 0.00**	78.85 ± 1.75**	89.12 ± 0.49**	20.5 ± 0.50**
ASH- 9	29.91 ± 0.16***	61.61 ± 1.06***	81.88 ± 0.46***	95.10 ± 0.74***	18.5 ± 0.50***
ASH- 10	28.86 ± 0.83***	57.85 ± 0.32***	80.77 ± 0.11***	91.68 ± 0.52***	19.0 ± 0.50***

DISCUSSION

Wound healing activities of the some selected synthesized compounds (ASH-2, 5, 9 & 10) were assessed against excision wound model[18-19] in albino rats. For this purpose the compounds were formulated as 2.5% w/w ointment using simple ointment IP as vehicle. Povidine iodine 5% w/w ointment used as reference standard drug.

The results of the present investigation indicate that all the four compounds on topical application in the form of ointment significantly promoted wound healing activity. The significant wound healing efficacy was evident by increase in rate of wound contraction and marked reduction in epithelization period.

Among the screened compounds for the wound healing study, the compound ASH-9 showed greater wound healing property (Almost equipotent to that of standard drug Povidine iodine) than the other tested compounds. The percentage wound closure on 18th day and period of epithelization were found to be closer to that of Povidine iodine treated group (percentage wound closure and epithelization time were 95.10 and 18.5 compared to 98.25 and 18.0 of the reference standard drug). The order of the wound healing efficacy of the test compound was found as ASH-9 > ASH-10 > ASH-5 > ASH-2. Results of wound healing activity indicate that, presence of halogen atom in the synthesized compounds favored the activity. However further studies are required to confirm this conclusion.

CONLUSION

Ten new N-aryl,5-Phenyl 1, 3, 4-Thiadiazoles compounds were synthesized. Analytical and spectral data were used to characterize all the synthesized compounds. Selected compounds were screened for wound healing activities. The results have shown that some compounds exhibited potent wound healing activity while the rest of the compounds exhibited moderate to mild wound healing activity.

ACKNOWLEDGMENT

The authors are thankful to Sri. T.M. Chandrashekaraiah, Secretary, T.M.A.E. Society, Harapanahalli through Principal, S.C.S College of Pharmacy, Harapanahalli, for providing necessary facilities to carry out this research work.

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