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SYNTHESIS AND QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR) STUDY OF NEW 3-ALLYL-5-SUBSTITUTED-3,4,5,6-TETRAHYDRO-2H-1,3,5-THIADIAZINE-2-THIONES OF A POTENTIAL ANTIMICROBIAL ACTIVITY

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تم تحضير خمسة عشر مركبا من ٣،٤،٥،٦ رباعي هيدرو ١،٥،٣ ثياديازين -٢ ثيون وذلك بتفاعل الليل امين مع ثانى كبرتيد الكربون وهيدروكسيد البوتاسيوم ثم فورمالدهيد الامين الاولى المناسب مثل ألكيل، أرالكيل أمين، جليسين، إل ألانين، إيثيل استرات الجلبسين. المركبات المذكورة تم اختبارها معمليا كمضادات للميكروبات (البكتريا موجبة وسالبة الجرام) وأيضا الكائنات الفطرية باستخدام طريقة قرص الاجار وتم دراسة العلاقة الكمية بين التركيب البنائي والفاعلية البيولوجية باستخدام log MIC للمركبات نحو الكائن الفطري (Scorplariopsis brevicoulis) وبعض الخصائص الطبيعية والكيميائية (Mr,L,Fr) للمشتقات عند الموضع (٥) وقد وجد تناسباً مستقيماً سلبياً بين log MIC و Mr,L وتناسباً مستقيماً موجباً مع Fr.

Fifteen new 3-allyl-5-substituted-3,4,5,6-tetrahydro-2H-1,3,5-thiadiazine-2-thiones were synthesized by the reaction of allylamine with carbon disulfide and potassium hydroxide, followed by formaldehyde and appropriate primary amine such as alkyl, aralkylamines, glycine, L-alanine or ethyl glycine ester. The title compounds were tested, in vitro, for antimicrobial activity against gram-positive bacteria (Bacillus cereus, Staphylococcus aureus, Micrococcus leuteus), Gram-negative bacteria (Escherichia coli, Serratia marcescens, Pseudomonas aeruginosa), and some fungi (Aspergillus flavus, Aspergillus niger, candida albicans, Geotrichum candidum, Scopulariopsis brevicaulis and Tricho-phyton rubrum), using agar disc method. Quantitative structure activity relationship study was performed using the log form of MIC against Scopulariopsis brevicaulis fungi and some physico-chemical descriptors (MR, L, and Fr) of substituents at N-5

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position. The log MIC were found to be negatively linearly correlated with MR and L and positively linearly correlated with Fr.

INTRODUCTION

Systemic mycosis in patients suffering from debilitating diseases such as neopliasis and in persons on long term total parentral nutrition[1] is becoming critical for the need of more and better antifungal agents. Compounds carrying the tetrahydro-1,3,5-thiadiazine-2-thione (THTT) skeleton have been reported to exhibit antibacterial[2-5], antifungal[6-9] and antiviral properties[10-13]. The antimicrobial activities of THTT may be through the production of isothiocyanate and/ or dithiocarbamic acids[3,14,15]. These findings motivated our interest to design new derivatives of THTT as antimicrobial agents. In our effort to shed light on the structural requirements for the antifungal and antibacterial activities of the 1,3,5-thiadiazine-2-thione nucleus, we prepared several new derivatives. Study of structural requirements was based on fixing of lipophilic substituent (allyl group) at N-3 position and incorporating different substituents at N-5 position[15-17]. The compounds were screened, and a variable antifungal and antibacterial activities were elaborated. Besides, we report classical quantitative structure-activity relationship studies (QSARs) using log MIC (µM/ml)against *Scopulariopsis brevicaulis* fungi and some electronic and steric descriptors of substituents at N-5 position. Results discussed below show optimum correlation when Fr, Mr and L descriptors are combined together in one model. The statistics of the fitting are impressive and indicate that the equation (model) derived is good predictor of activity.

EXPERIMENTAL

Materials and equipments

Melting points were determined on an electrothermal melting point apparatus [Stuart Scientific, UK], and are uncorrected. Precoated silica gel plates (kiesel gel 0.25 mm, 60G F254, Merck) were used for thin layer chromatography. Developing solvent system of chloroform/methanol (10:3) was used and the spots were detected by ultraviolet light. IR spectra (KBr disc) were recorded on IR-470 Shimadzu spectrometer, Japan. ^{1}H-NMR Spectra were scanned on a Varian EM-360 L NMR spectrometer (60 MHz) USA at Faculty of Pharmacy Assiut University. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard, using $CDCl_3$ as a solvent. Elemental analyses were performed at the Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt. Antimicrobial activity was performed at Mycology center AUMC, Department

of Botany, Faculty of Science, Assiut University, Assiut, Egypt.

General procedure for synthesis of 3-allyl-5-substituted tetrahydro-2H-1,3,5-thiadiazine-2-thiones; (4a-o)[4,5]

Carbon disulfide (60 mmol, 3.6 ml) was added portionwise to a stirred mixture of the allylamine **1** (10 mmol, 0.75 ml) and potassium hydroxide (40%, 20 mmol, 1.4 ml). The reaction mixture was stirred for 3 h. at ambient temperature. To the reaction mixture, which contains the potassium dithiocarbamates **2**, formaldehyde solution (35%, 22 mmol, 1.63 ml), was added and the stirring was continued for further 1 h. The resulting clear solution of **3** was added portionwise during 15 min to a stirred solution of the appropriate alkylamine, aralkylamine, glycine, L-alanine or ethyl glycine ester (10 mmol) in phosphate buffer (pH 7.8, 20 ml). After stirring for 6 h. at ambient temperature, the reaction mixture was acidified with dilute hydrochloric acid (5%, ~ 15-18 ml) to pH 2 and the stirring was continued for further 30 min. The formed precipitate was collected by filtration, washed with 0.5% hydrochloric acid and dried. The crude solid was crystallized from methanol-chloroform (1:1) to afford **4a-o** Yields, physical and spectral data are given in Tables I and II.

Antimicrobial Activity

Organisms, culture conditions, and antimicrobial activity

Six pathogenic fungal species were used in the present study: Aspergillus flavus, Aspergillus niger, candida albicans, Geotrichum candidum, Scopulariopsis brevicaulis and Trichophyton rubrum (Robin) Berkhout (a cause of candidiasis), Candida albicans and Trichophyton rubrum were isolated from clinical cases in the Assiut University hospitals. For antibacterial activity three gram-positive bacteria (Bacillus cereus, staphylococcus aureus, Micrococcus leuteus), and three gram-negative bacteria (Escherichia coli, Serratia marcescens, pseudomonas aeruginosa) were used. Spore suspension in sterile distilled water was prepared from 3-5 days old culture of the test fungi growing on SAD medium. The final spore concentration was 5x104 spores/ml. About 20 ml of growth medium was introduced on sterilized plates of 9 Cm diameter and inoculated with 1ml of spore suspension. Plates were shaken gently to homogenize the inoculum. Antifungal activity of the tested compounds was performed by the standard agar disk diffusion method18 as follow: Sterile 6 mm filter paper disks (Whatman) were impregnated with 5 µl solutions of the tested compounds (10 mg/ml in DMSO). In addition, other disks were impregnated with the solvent (DMSO) and served as control. The impregnated disks were then dried for 1 hour and placed in the center of

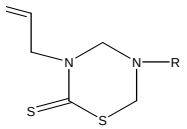
each plate. The seeded plates were incubated at 30 ± 2°C for 7 days. The radius of the inhibition zones (in mm) were measured at successive intervals during the incubation period. Triplicate set were applied for each treatment. Results are given in Table III in comparison to reference drugs (clotrimazole and chloramphenicol) as antifungal and antimicrobial respectively.

For all compounds except the weak active compounds **4l**, **4n**, and **4o**, the tube dilution method was used for determination of minimal inhibitory concentrations (MIC). The concentrations of the compounds in tubes were 1, ½ and ¼ µmole/ml, respectively[7].

Table 1: Physicochemical data of the newly synthesized derivatives.

Compd. No	R	Yield %	Formula	M.p. °C	Elemental analysis (Calc/found)			
					C	H	N	S
4a	CH_3	45	$C_7H_{12}N_2S_2$	61-3	44.65 44.50	6.42 6.23	14.88 14.89	
4b	C_2H_5	60	$C_8H_{14}N_2S_2$	48-50	47.49 48.24	6.97 7.05	13.84 14.23	
4c	n-C_3H_7	57	$C_9H_{16}N_2S_2$ .1/2H_2O	36-8	48.00 47.23	7.56 7.08	12.44 12.15	28.44 27.86
4d	*i*-C_3H_7	65	$C_9H_{16}N_2S_2$	44-6	49.96 50.45	7.45 6.92	12.95 13.09	29.64 29.12
4e	n-C_4H_9	62	$C_{10}H_{18}N_2S_2$	43-4			12.16 12.07	27.84 27.27
4f	i-butyl	60	$C_{10}H_{18}N_2S_2$	liquid				
4g	t- C_4H_9	55	$C_{10}H_{18}N_2S_2$	99-101	52.13 51.32	7.87 7.51	12.16 12.02	
4h	n-C_5H_{11}	70	$C_{11}H_{20}N_2S_2$ $2H_2O$	52-4			9.99 9.94	22.87 22.14
4i	n-C_6H_{13}	70	$C_{12}H_{22}N_2S_2$.1/2 H_2O	56-8			10.48 10.78	23.97 24.04
4j	CH_2COOH	65	$C_8H_{12}N_2O_2S_2$. 1/2 H_2O	132-4	39.83 40.08	5.39 4.91	11.62 11.78	26.55 26.17
4k	$CH(CH_3)COOH$	60	$C_9H_{14}N_2O_2S_2$	111-13	43.88 43.37	5.73 5.55	11.37 11.25	26.03 25.91
4l	$CH_2COOC_2H_5$	45	$C_{10}H_{16}N_2O_2S_2$	100-02	46.13 45.12	6.19 6.04	10.76 10.73	24.63 24.69
4m	CH_2=$CHCH_2$	52	$C_9H_{14}N_2S_2$	54-6	50.43 50.86	6.58 6.66	13.07 13.31	
4n	C_6H_5-CH_2	55	$C_{13}H_{16}N_2S_2$	51-3	59.05 59.23	6.10 6.05	10.59 10.53	24.25 23.16
4o	C_6H_5-$CH(CH_3)$	87	$C_{14}H_{18}N_2S_2$	118-20	60.39 59.94	6.52 6.47	10.06 10.07	23.03 23.33

Table II: The ^{1}H-NMR chemical shifts of synthesized compounds in $CDCl_3$



[4a-o]

No	R	Allyl-N-3	CH_2 at C4 and C6	R-N-5
4a	CH_3	4.8 (d, 2H, CH_2-N), 5.3 (d, 1H, =CH_2), 5.6 (d, 1H, =CH_2), 6.4-5.8 (m, 1H, =CH)	4.5 (s, 2H) 4.6 (s, 2H)	2.7 (s, 3H, CH_3)
4b	C_2H_5	4.8 (d, 2H, CH_2-N), 5.3 (d, 1H, =CH_2), 5.5 (d, 1H, =CH_2), 6.4-5.7 (m, 1H, =CH)	4.5 (s, 2H) 4.6 (s, 2H)	1.2 (t, 3H, $CH_2C\underline{H}_3$), 2.9 (q, 2H, $C\underline{H}_2CH_3$)
4c	n-C_3H_7	4.8 (d, 2H, CH_2-N), 5.3 (d, 1H, =CH_2),5.5 (d, 1H, =CH_2), 6.4-5.7 (m, 1H, =CH)	4.4 (s, 2H) 4.6 (s, 2H)	1.0 (t, 3H, $C\underline{H}_3$), 1.9-1.3 (m, 2H, $CH_2C\underline{H}_2$), 2.8 (t, 2H, $C\underline{H}_2CH_2$)
4d	*i*-C_3H_7	5.1 (d, 2H, CH_2-N), 5.6 (d, 1H, =CH_2),5.8 (d, 1H, =CH_2), 6.8-6.0 (m, 1H, =CH)	4.7 (s, 2H) 4.8 (s, 2H	1.3 (d, 6H, 2($C\underline{H}^3$), 3.7-3.2 (m, 1H, $C\underline{H}$)
4e	n-C_4H_9	4.8 (d, 2H, CH_2-N), 5.3 (d, 1H, =CH_2), 5.5 (d, 1H, =CH_2) 6.7-5.8 (m, 1H, =CH)	4.5 (s, 2H) 4.5 (s, 2H)	1.00 (t, 3H, $C\underline{H}_3$), 2.4-1.1 (br.m,4H, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 2.9 (t, 2H, N5-$C\underline{H}_2$)
4f	i- C_4H_9	5.1 (d, 2H, CH_2-N) 5.6 (d,1H, =CH_2) 5.8 (d, 1H, =CH_2) 6.8-5.1 (m, 1H, =CH)	4.7 (s, 2H) 4.8 (s, 2H)	1.0 (d, 6H, 2 $C\underline{H}_3$), 2.3-1.4 (m,1H, CH), 2.8 (d, 2H, N5-$CH_{2)}$
4g	t- C_4H_9	4.8 (d, 2H, CH_2-N), 5.3 (d, 1H, =CH_2), 5.5 (d, 1H, =CH_2), 6.4-5.8 (m, 1H, =CH)	4.6 (s, 2H) 4.7 (s, 2H)	1.3 (s, 9H, 3 CH_3)
4h	n- C_5H_{11}	4.8 (d, 2H, CH_2-N), 5.3 (d,1H, =CH_2), 5.5 (d, 1H, =CH_2), 6.4-5.7 (m, 1H, =CH)	4.4 (s, 2H) 4.5 (s, 2H)	0.9 (t, 3H, $C\underline{H}_3$), 1.9-1.1 (m, 6H, 3 $C\underline{H}_2$), 2.8 (t, 2H, N5-$C\underline{H}_2$)
4i	n-C_6H_{13}	4.8 (d, 2H, CH_2-N), 5.3 (d,1H, =CH_2), 5.5 (d, 1H, =CH_2), 6.4-5.7 (m, 1H, =CH	4.4 (s, 2H) 4.5 (s, 2H)	0.9 (t, 3H, $C\underline{H}_3$), 1.9-1.1 (m, 6H, 4 $C\underline{H}_2$), 2.8 (t, 2H, N5-$C\underline{H}_2$)
4j	CH_2COOH	4.8 (d, 2H,CH_2-N),5.3 (d, 1H, =CH_2),5.5 (d, 1H, =CH_2) 6.4-5.8 (m, 1H, =CH)	4.5 (s, 2H) 4.6 (s, 2H)	3.7 (s, 2H, $C\underline{H}_2$ COOH), 12 (br. s, 1H, exch. COO$\underline{H}$)
4k	(-)CH (CH_3)COOH	4.9 (d, 2H, CH_2-N),5.3 (d, 1H, =CH_2),5.6 (d, 1H, =CH_2), 6.5-5.8 (m, 1H, =CH)	4.7 (s, 4H)	1.5 (d, 3H, CH_3), 4.0 (q, 2H, $C\underline{H}CH_3$), 10.9 (br. s, 1H, exch. COO$\underline{H}$)
4l	$CH_2COOC_2H_5$	4.8 (d, 2H, CH_2-N), 5.3 (d, 1H, =CH_2),5.5 (d, 1H, =CH_2), 6.4-5.8 (m, 1H, =CH)	4.5 (s, 2H) 4.6 (s, 2H)	4.3 (q,2H, $COOC\underline{H}_2CH_3$), 3.7 (s, 2H, $C\underline{H}_2COOC_2H_5$), 1.3 (t,3H, $COOCH_2C\underline{H}_3$)
4m	CH_2=$CHCH_2$	4.8 (d, 2H, CH_2-N),5.3 (d, 1H of =CH_2),5.5 (d, 1H of =CH_2),6.5-5.7 (m, 1H of =CH)	4.5 (s, 2H) 4.6 (s, 2H)	3.5 (d, 2H, N5-CH_2), 5.3 (d, 1H of =CH_2), 5.5 (d, 1H of =CH_2), 6.5-5.7 (m, 1H of =CH)
4n	C_6H_5-CH_2	4.7 (d, 2H, CH_2-N),5.3 (d, 1H, =CH_2),5.4 (d, 1H, = CH_2), 6.4-5.7 (m, 1H, =CH)	4.5 (s, 4H)	7.5 (s, 5H, $C_6\underline{H}_5$-CH_2), 4.1 (s, 2H, C_6H_5-$C\underline{H}_2$)
4o	(±) C_6H_5-H(CH_3)	5.1 (d, 2H, CH_2-N),5.4 (d, 1H, =CH_2),5.7 (d, 1H, =CH_2), 6.7-6.1 (m, 1H, =CH)	4.5-4.3 (m, 5H, $2CH_2$ and N5-CH)	1.6 (d, 3H, $C_6H_5CH(C\underline{H}_3)$, 7.9 (s, 5H, $C_6\underline{H}_5$),

Table III: Antimicrobial activity of the tested compounds (expressed as the diameter of the inhibition zone[a]).

No	*Aspergillus flavus*	*Aspergillus niaer*	*Candida albicans*	*Geotrichum candidum*	*Scopulariopsis brevicaulis*	*Trichophyton rubrum*	*Bacillus cereus*	*Micrococcus luteus*	*Staphylococcus aureus*	*Escherichia coli*	*Serratia marcescens*	*Pseudomonas aeruginosa*
4a	20	20	21	24	14	20	20	50	18	25	14	-
4b	7	21	20	20	14	15	20	32	15	20	12	10
4c	14	17	15	15	20	14	19	40	11	25	10	-
4d	-	16	17	18	16	12	20	30	16	20	6	10
4e	15	20	14	12	15	13	15	35	10	15	10	13
4f	13	20	13	12	13	11	15	30	12	20	10	7
4g	12	-	13	14	12	11	15	20	13	20	15	10
4h	11	11	11	10	11	11	11	15	10	13	7	7
4i	-	15	12	12	12	-	7	22	10	10	6	-
4j	13	20	13	20	13	14	18	50	17	26	10	7
4k	20	22	15	12	20	15	20	26	15	22	16	12
4l	-	-	-	-	-	-	13	30	10	17	7	-
4m	-	20	10	13	13	11	19	26	12	16	7	-
4n	-	-	9	-	-	-	-	10	6	10	-	-
4o	-	-	6	-	-	-	-	p.i.	-	-	-	-
Ref.1	-	-	-	-	-	-	50	52	30	40	-	30
Ref.2	23	22	30	20	22	13	-	-	-	-	-	-

- [a)]Average of three observations.
- Inhibition zone in mm. Disc diameter is 6 mm.
- "-" no inhibition zone.
- Ref. 1 Chloramphenicol as antibacterial.
- Ref. 2 Clotrimazole as antifungal.

Quantitative structure activity relationship

The inhibition values

Quantitative structure-activity rela-tionship study (QSARs) was performed using physicochemical activity relationship methods (PAR)[19]. The minimal inhibitor concentrations (MIC) in μM/ml against *Scopulariopsis brevicaulis* fungi were adopted. These values were converted to their log form and used in the present investigations.

The descriptors

hydrophobic effect was treated by use of fragmental constants, Fr^{20}, instead of Pi-value. The former was calculated by summing structural elements rather than substitution to calculate the log P value of an analog. Bulk substituent constants were employed using the molar refraction,

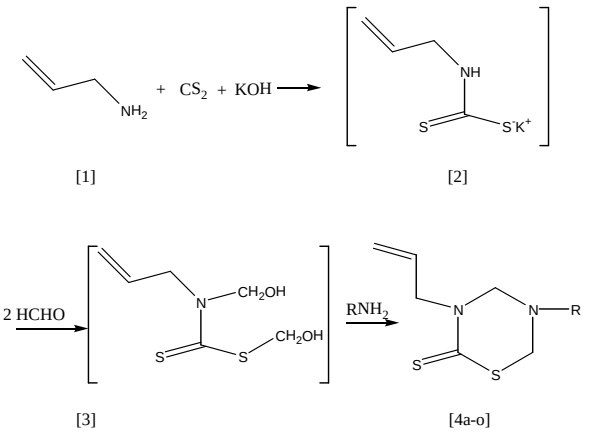
MR[21&22]. In addition, Sterimol-L values[23] (Steric length parameter) were measured along the substitution point bond axis.

RESULTS AND DISCUSSION

Chemistry

The target compounds were synthesized by the reaction of allylamine (**1**) with carbon disulphide and potassium hydroxide. The resulting dithiocarbamate potassium salt (**2**) without isolation was then allowed to react with formaldehyde to give (**3**) which was not isolated. The latter derivative was then allowed to react with the appropriate alkylamine, aralkylamine, glycine, L-alanine, or ethyl glycine ester in presence of phosphate buffer (pH = 7.8) to give (**4a-o**) (see Scheme 1). It was suggested that the reaction proceeds through the formation of the intermediates (**2**) and (**3**) in situ[3-6]. Structures of the synthesized compounds were verified on the bases of spectral and elemental methods of analyses. Table 1, shows the physicochemical constants of the newly synthesized derivatives (**4a-o**). All spectral data are in accordance with the expected structures. The IR spectra of compounds **4a-o** showed bands at 2840-2960 cm^{-1} (aliphatic C-H stretching); 3030-3060 cm^{-1} (olefinic C-H stretching) and at about 1420-1455 cm^{-1} (C=S stretching). Moreover, compounds **4j** and **4k** showed the characteristic stretching absorption of the OH group at 2500-3200 cm^{-1} and C=O at 1705-1715 cm^{-1}. Compound **4l** showed the ester C=O stretching at 1745 cm^{-1} and C-O stretching very strong band at 1240 cm^{-1}.

In the ^{1}H-NMR spectra, a common pattern was found for the methylenes of C4, C6 and for allyl group at N-3 [δ 4.74-5.08 (d, 2H, CH_2-N), 5.25-5.58 (d, 1H, =C$\underline{H}_2$), 5.43-5.83 (d, 1H, =C$\underline{H}_2$), 5.7-6.4 (m, 1H, =CH-) in all derivatives. The characteristic differences in sets and patterns were attributed to the N-5-side chain (Table II).



[1] [2] [3] [4a-o]

Scheme 1: R= CH_3 (a), C_2H_5 (b), n-C_3H_7 (c), i-C_3H_7 (d), n-C_4H_9 (e), i-C_4H_9 (f), tert-C_4H_9 (g), n-C_5H_{11} (h), C_6H_{13}(i), CH_2COOH (j), $CH(CH_3)COOH$ (k), -$CH_2COOC_2H_5$ (l), CH_2=$CHCH_2$ (m), C_6H_5-CH_2 (n), C_6H_5-CH (CH_3) (o).

Antimicrobial Activity

The synthesized compounds (**4a-o**) were tested for their antifungal activity *in vitro* against *Aspergillus flavus, Aspergillus niger, Candida albicans, Geotrichum candidum, Scopulariopsis brevicaulis and Trichophyton rubrum* fungi using the standard agar diffusion method[17] in comparison to clotrimazole as a standard drug. Table III shows the results of the antifungal activity of the tested compounds expressed as the inhibition zone in mm. Also, the same compounds were tested, *in vitro*, for their antibacterial activity against gram-positive bacteria *(Bacillus cereus, Staphylococcus aureus, Micrococcus leuteus),* and gram-negative bacteria *(Escherichia coli, Serratia marcescens, Pseudomonas aeruginosa)* using chloramphenicol as a standard drug. The antimicrobial study explored variable activities according to variation of substituents at N-5 position of the THTT moiety. The results clearly indicate that the introduction of a variety of groups at N-5 gave good antifungal and moderate antibacterial compounds **4a-k** and **4m**, relative to the reference clotrimazole or chloramphenicol respectively. However compounds **4l, 4n,** and **4o** revealed no antifungal and weak antibacterial activity**.**

For all compounds except the weak active compounds **4l**, **4n**, and **4o**, the tube dilution method was used for determination of minimal inhibitory concentrations (MIC) Table IV. The concentrations of the compounds in tubes were 1, ½ and ¼ µM/ml, respectively[7].

Table IV: Antimicrobial activity of the tested compounds (expressed as the MIC in µM/ml).

No	*Aspergillus flavus*	*Aspergillus niger*	*Candida albicans*	*Geotrichum candidum*	Scopulariopsis brevicaulis	*Trichophyton rubrum*	Bacillus *cereus*	Micrococcus *luteus*	Staphylococcus Aureus	Escherichia *coli*	Serratia *marcescens*	*Pseudomonas aeruginosa*
4a	13.27	13.27	26.55	53.1	26.55	13.27	26.55	13.27	26.55	-	13.27	-
4b	49.42	12.35	12.35	49.42	24.71	12.35	24.71	12.35	49.42	12.35	-	49.42
4c	23.11	23.11	11.55	-	23.11	11.55	46.22	-	46.22	11.55	-	-
4d	-	23.11	11.55	23.11	23.11	11.55	23.11	23.11	46.22	11.55	23.11	-
4e	21.7	10.85	21.7	43.4	10.85	10.85	43.4	10.85	43.4	10.85	10.85	-
4f	43.4	10.85	21.7	21.7	21.7	21.7	43.4	10.85	43.4	10.85	-	-
4g	43.4	-	10.85	21.7	21.7	21.7	43.4	10.85	43.4	10.85	10.85	-
4h	40.91	40.91	40.91	-	10.23	10.23	40.91	10.23	40.91	10.23	-	-
4i	-	38.68	-	19.34	9.67	-	-	9.67	38.68	-	-	-
4j	-	10.76	-	-	10.76	10.76	21.5	10.76	21.5	-	10.76	-
4k	10.16	-	10.16	40.64	10.16	10.16	40.46	10.16	40.46	-	-	10.16
4m	-	11.66	-	-	23.32	23.32	46.65	11.66	46.65	11.66	11.66	-

Quantitative structure activity relationship

The structural details of the synthesized compounds used in this investigation are given in scheme 1. The antifungal activity against *Scopulariopsis brevicaulis* in log unit (log MIC) of this set are recorded in Table V. This table also contains the values of the descriptor parameters Fr, MR, and L. Results shown in Table VI proved weak correlation of the independent variables with each others and weak to moderate correlation with the dependent variable.

Table V: Dependent and independent values of the compounds.

Compd. No.	Log MIC	Fr*	MR**	L**
4a	1.42	0.70	5.65	0.30
4b	1.39	1.40	10.30	4.11
4c	1.36	1.93	14.96	5.05
4d	1.36	1.63	14.96	4.11
4e	1.03	2.46	19.59	6.17
4f	1.34	2.33	19.59	5.02
4g	1.34	2.11	19.62	4.11
4h	1.01	2.96	24.26	7.11
4i	0.99	3.49	26.02	8.05
4j	1.03	-0.55	11.88	4.91
4k	1.01	-0.02	16.52	4.91
4m	1.37	1.46	14.49	4.29

* Fr values are calculated using R. Rekker's equation (ref 20).

**MR and L are obtained from literature (refs. 21 and 22).

Table VI: Correlation matrix for the intercorrelation of various molecular descriptors.

log MIC	Log MIC	Fr	MR	L
	1.000			
Fr	-0.075	1.000		
MR	-0.582	0.748	1.000	
L	-0.776	0.634	0.855	1.000

For modeling antifungal activity against *Scopulariopsis brevicaulis* fungi, a stepwise regression analysis was carried out using maximum R^2-method[23]. The results obtained are presented in Table VII. A perusal of Table VII shows that only one parameter alone doesn't give good results, while the bi-parametic regression expression involving MR and Fr revealed statistically significant results. On the other hand, when MR is coupled with the Fr and L, regression obtained was found superior than the bi-parametic model and the model resulted is shown below:

Equation

$$\log MIC = 0.1272\ Fr - 0.0101\ MR - 0.1333\ L + 1.8543$$

n= 12, S.E.= 0.0646, R= 0.955,
F= 27.56 and Q= 14.783

Where, n is the number of compounds used, S.E. is the standard error of estimation, R is multiple correlation coefficient. F is F-statistics. From the model the L and Fr descriptors are the major factors for the exhibition of antifungal activity against

Scopulariopsis brevicaulis fungi. i.e The bulkiness of the substituent has smaller factor for the activity. Also, the above equation shows that the coefficients of MR and L are negative while the coefficient of Fr is positive. That is the log MIC is negatively linearly correlated with MR and L and positively linearly correlated with Fr. In other words as the decrease in hydrophobicity and the increase in length of the substituent at N-5 position increase the antifungal activity against *Scopulariopsis brevicaulis* fungi. That compounds, with substituent at N-5 position of 4C-6C length (**4e**, **4h, 4i**) or contain hydrophilic carboxylic group (**4j**, **4k**), are most active (MIC values 9.67-10.85 μM/ml).

Table VII: Regression parameters and quality of correlation for modeling log MIC (μmole/ml) activity.

Model No.	Param. Used	Ai = 1,2,3	B intercept	S.E.	Corr. Coef. (R)	R^2	F-ratio	Q= R/S.E.
1a	Fr	-0.0119	1.2418	0.1939	0.075	0.0056	0.06	0.386
1b	L	-0.1018	1.7382	0.1226	0.776	0.602	15.13	6.329
1c	MR	-0.0187	1.5307	0.1580	0.582	0.339	5.13	3.683
2a	Fr L	0.0597 -0.1153	1.7285	0.1028	0.865	0.748	13.39	8.414
2b	MR L	0.0097 -0.1357	1.7500	0.1252	0.792	0.627	7.55	6.326
2c	Fr MR	0.0844 -0.0271	1.5582	0.1320	0.765	0.585	6.34	5.795
3	Fr MR L	0.1272 0.0101 -0.1333	1.8543	0.0646	0.955	0.91	27.56	14.78

Conclusion

In this work a series of 3-allyl-5-substituted-2H-3,4,5,6-tetrahydro-1,3, 5-thiadiazine-2-thione derivatives were synthesized and tested for antimicrobial activity. The results indicated that the antifungal activity against *Scopulariopsis brevicaulis* fungi could be successfully modeled by the combination of MR, Fr and L parameters. The QSAR model revealed that the decrease in hydrophobicity and the increase in length of the substituent at N-5 position increase the antifungal activity against *Scopulariopsis brevicaulis* fungi.

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