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5-(1*H*-indol-3-ylmethyl)-N-(substituted phenyl)-1, 2, 4-thiadiazol-2-amine derivatives: Synthesis and biological screening

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ABSTRACT

A number of new 5-(1*H*-indol-3-ylmethyl)-N-(substituted phenyl)-1, 2, 4-thiadiazol-2-amine derivatives (1-10) were synthesized and evaluated for their antibacterial and antifungal activity. The titled compounds (1-10) were obtained by cyclization of 2-(1*H*-indol-3-yl acetyl)-N-(substituted pheynyl) hydrazine carbothioamide in presence of conc. sulphuric acid. The structures of newly synthesized compounds were characterized by spectral and elemental analyses. Compounds (1 and 4) showed 80% and 72% inhibition respectively against *S. aureus* while as compounds (2, 3 and 4) showed 76% inhibition against *E.coli*. Compounds (1, 4 and 8) showed 70%, 85% and 65% inhibition respectively against *C. albicans*.

Key words: 1, 3, 4-thiadiazole derivatives and antimicrobial activity.

INTRODUCTION

Microbial diseases are very common all over the world. Currently used antimicrobial agents are not effective due to resistance developed by microbes, and therefore it is an ongoing effort to synthesize new antimicrobial agents. Antimicrobials reduce or completely block the growth and multiplication of bacteria. They have transformed our ability to treat infectious diseases such as pneumonia, meningitis, tuberculosis, malaria and AIDS. Derivatives of 1, 3, 4-thiadiazole nucleus system found to have diverse biological activities such as antibacterial[1], anti-inflammatory[2], antitubercular[3], anticancer[4], antifungal[5] and antiviral[6]. A large number of reports on their synthesis and biological activities have appeared during the last three years. In our previous research on anticonvulsants, different thiadiazole moieties were selected for the synthesis of anticonvulsant agents[7, 8, 9, 10]. Herein, we with to report the synthesis, antibacterial and fungicidal activities of some new 5-(1*H*-indol-3-ylmethyl)-N-(substituted phenyl)-1, 3, 4-thiadiazol-2-amine derivatives.

MATERIAL AND METHODS

All the solvents were of LR grade and were obtained from Merck, CDH, and s.d. fine chemicals. Melting points were determined in open capillary tubes and are uncorrected. All the compounds were subjected to elemental analysis and the measured values agreed within ±0.4% with the calculated ones. Thin layer chromatography was performed on Silica gel G (Merck). The spots were recorded in KBr pellets on (BIO-RAD FTS 135) WIN-IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker model DPX 300 FT-NMR spectrometer in ($CDCl_3$) using tetramethylsilane (Me_4Si) TMS as an internal Standard. The chemical shifts are reported in δ ppm scale.

Synthetic study

General method for syntheses of 5-(1*H*-indol-3-yl methyl)-N-(substituted phenyl)1, 3, 4-thiadiazol-2-amines[1-10]. The synthesis of compounds[1-10] was accomplished by etherification of Indol-3-acetice acid, which in presence of hydrazine hydrate gave its hydrazide. The hydrazide on treatment with arylilothiocyanates was converted into their respective. The hydrazide on treatment

with arylisothiocyanates was converted into their respective carbothioamide derivatives according to the literature protocol[11]. Concentrated sulphuric acid (5 ml) was taken in a conical flask, to it was added 2-(H-indol-3-ylacetyl)-N-phenyl hydrazine carbothioamide (0.004 moles; 1.23 gm) in small portion over a period of two hours with stirring while maintaining the temperature to about 0-5°C. When reaction was completed, the mixture was poured over crushed ice. Precipitated solid[1] thus obtained was filtered, washed with water, dried at room temperature, and recrystallized from absolute ethanol. The compounds[2-10] were also synthesized by similar method using reagents in proper moles. The synthetic protocol of the compounds is shown in scheme-1. The physical constants of the titled compounds are presented in Table 1.

5-(1*H*-indol-3-yl methyl)-*N*-Phenyl-1, 3, 4-thiadiazol-2-amine. (1)

FT-IR (KBr, V_{max} in cm^{-1}): 3568 (NH Str.), 3211 (Ar-CH), 2340 (CH_2), 1594 (C=C), 1032 (N-N), 604 (C-S-C). ^{1}H-NMR (DMSO-d_6) δ ppm: 10.22 (s, 1H, NH), 9.52 (s, 1H, NH indole), 6.66-8.70 (m, 9H, Ar-H), 6.66 (s, 1H, CH indole), 4.25 (s, 2H, CH_2).

5-(1*H*-indol-3-yl methyl)-*N*-(2-chlorophenyl)-1, 3, 4-thiadiazol-2-amine. (2)

FT-IR (KBr, V_{max} in cm^{-1}): 3694 (NH Str.), 2921 (Ar-CH), 2283 (CH_2), 1585 (C=N), 1503 (C=C), 943 (N-N), 743 (C-S-C), 699 (C-Cl). ^{1}H-NMR (DMSO-d_6) δ ppm: 10.23 (s, 1H, NH), 8.31 (s, 1H, NH indole), 6.50-8.91 (m, 8H, Ar-H), 6.50 (s, 1H, CH indole), 4.03 (s, 2H, CH_2).

5-(1*H*-indol-3-yl methyl)-*N*-(3-chlorophenyl)-1, 3, 4-thiadiazol-2-amine. (3)

FT-IR (KBr, V_{max} in cm^{-1}): 3600 (NH Str.), 2978 (Ar-CH), 2190 (CH_2), 1604 (C=N), 1594 (C=C), 963 (N-N), 723 (C-S-C), 668 (C-Cl). ^{1}H-NMR (DMSO-d_6) δ ppm: 9.96 (s, 1H, NH), 8.76 (s, 1H, NH indole), 6.78-8.03 (m, 8H, Ar-H), 6.56 (s, 1H, CH indole), 3.89 (s, 2H, CH_2).

5-(1*H*-indol-3-yl methyl)-*N*-(2-chlorophenyl)-1, 3, 4-thiadiazol-2-amine. (4)

FT-IR (KBr, V_{max} in cm^{-1}): 3678 (NH Str.), 2959 (Ar-CH), 2083 (CH_2), 1591 (C=N), 1569 (C=C), 950 (N-N), 779 (C-S-C), 693 (C-Cl). ^{1}H-NMR (DMSO-d_6) δ ppm: 10.48 (s, 1H, NH), 8.92 (s, 1H, NH indole), 6.45-8.60 (m, 8H, Ar-H), 6.32 (s, 1H, CH indole), 4.45 (s, 2H, CH_2).

5-(1*H*-indol-3-yl methyl)-*N*-(2-methyl phenyl)-1, 3, 4-thiadiazol-2-amine. (5)

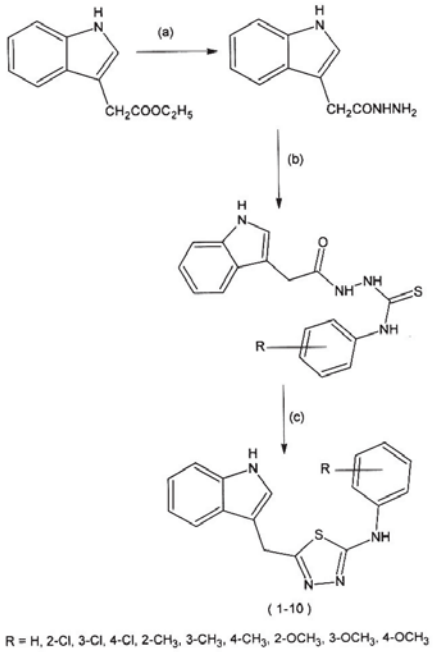
FT-IR (KBr, V_{max} in cm^{-1}): 3633 (NH Str.), 3263 (Ar-CH), 2921 (CH_3), 2386 (CH_2), 1614 (C=N), 1585 (C=C), 1030 (N-N), 616 (C-S-C). ^{1}H-NMR (DMSO-d_6) δ ppm: 11.02 (s, 1H, NH), 9.23 (s, 1H, NH indole), 7.84 (s,1H, CH indole), 6.98-7.81 (m, 8H, Ar-H), 4.33 (s, 2H, CH_2), 1.51 (s, 3H, CH_3).

5-(1*H*-indol-3-yl methyl)-*N*-(3-methyl phenyl)-1, 3, 4-thiadiazol-2-amine. (6)

FT-IR (KBr, V_{max} in cm^{-1}): 3598 (NH Str.), 3278 (Ar-CH), 2893 (CH_3), 2298 (CH_2), 1684 (C=N), 1592 (C=C), 1061 (N-N), 656 (C-S-C). ^{1}H-NMR (DMSO-d_6) δ ppm: 10.87 (s, 1H, NH), 9.39 (s, 1H, NH indole), 7.04 (s,1H, CH indole), 6.92-7.94 (m, 8H, Ar-H), 4.96 (s, 2H, CH_2), 1.84 (s, 3H, CH_3).

5-(1*H*-indol-3-yl methyl)-*N*-(4-methyl phenyl)-1, 3, 4-thiadiazol-2-amine. (7)

FT-IR (KBr, V_{max} in cm^{-1}): 3667 (NH Str.),



Scheme 1: Reagents and conditions (a) $NH_2.NH_2.H_2O$/Ethanol, reflux, 10h, (b) ArNCS/ Ethanol, reflux 5h (c) conc. H_2SO_4

3198 (Ar-CH), 2900 (CH_3), 2297 (CH_2), 1603 (C=N), 1596 (C=C), 1059 (N-N), 603 (C-S-C). ^{1}H-NMR (DMSO-d_6) δ ppm: 11.98 (s, 1H, NH), 9.89 (s, 1H, NH indole), 7.45 (s,1H, CH indole), 6.58-7.61 (m, 8H, Ar-H), 4.58 (s, 2H, CH_2), 1.38 (s, 3H, CH_3).

5-(1*H*-indol-3-yl methyl)-*N*-(2-methoxy phenyl)-1, 3, 4-thiadiazol-2-amine. (8)

FT-IR (KBr, V_{max} in cm^{-1}): 3519 (NH Str.), 3296 (Ar-CH), 2365 (CH_2), 1649 (C=N), 1149 (C-OCH_3), 1030 (N-N), 605 (C-S-C). ^{1}H-NMR (DMSO-d_6) δ ppm: 11.07 (s, 1H, NH), 8.41 (s, 1H, NH indole), 7.08-7.52 (m, 8H, Ar-H), 5.34 (s,1H, CH indole), 4.39 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3).

5-(1*H*-indol-3-yl methyl)-*N*-(3-methoxy phenyl)-1, 3, 4-thiadiazol-2-amine. (9)

FT-IR (KBr, V_{max} in cm^{-1}): 3478 (NH Str.), 3267 (Ar-CH), 2330 (CH_2), 1684 (C=N), 1582 (C=C), 1102 (C-OCH_3), 1079 (N-N), 626 (C-S-C). ^{1}H-NMR (DMSO-d_6) δ ppm: 11.92 (s, 1H, NH), 8.72 (s, 1H, NH indole), 6.83-7.04 (m, 8H, Ar-H), 5.83 (s,1H, CH indole), 4.96 (s, 2H, CH_2), 3.05 (s, 3H, OCH_3).

5-(1*H*-indol-3-yl methyl)-*N*-(4-methoxy phenyl)-1, 3, 4-thiadiazol-2-amine. (10)

FT-IR (KBr, V_{max} in cm^{-1}): 3594 (NH Str.), 3261 (Ar-CH), 2393 (CH_2), 1662 (C=N), 1563 (C=C), 1148 (C-OCH_3), 1094 (N-N), 598 (C-S-C). ^{1}H-NMR (DMSO-d_6) δ ppm: 11.83 (s, 1H, NH), 8.59 (s, 1H, NH indole), 7.04-7.27 (m, 8H, Ar-H), 5.22 (s,1H, CH indole), 3.99 (s, 2H, CH_2), 4.87 (s, 3H, OCH_3).

Table 1: Physical constants of synthesized compounds

Compd. No.	R	Molecular Formula	m.p. (°C)	% Yield	% Analyses Calculated (Found)N
1	H	$C_{17}H_{14}N_4S$	136-139	82	18.29(18.69)
2	2-Cl	$C_{17}H_{13}ClN_4S$	152-155	75	16.44(16.57)
3	3-Cl	$C_{17}H_{13}ClN_4S$	165-168	68	16.44(16.21)
4	4-Cl	$C_{17}H_{13}ClN_4S$	135-138	71	16.44(16.84)
5	2-CH_3	$C_{18}H_{16}N_4S$	168-171	65	17.49(17.79)
6	3-CH_3	$C_{18}H_{16}N_4S$	120-123	71	17.49(17.64)
7	4-CH_3	$C_{18}H_{16}N_4S$	142-145	72	17.49(17.20)
8	2-OCH_3	$C_{18}H_{16}N_4OS$	140-143	73	16.65(16.94)
9	3-OCH_3	$C_{18}H_{16}N_4OS$	170-173	68	16.65(17.12)
10	4-OCH_3	$C_{18}H_{16}N_4OS$	129-131	79	16.65(16.95)

Percentage analyses for N were in agreement with the theoretical value

Table 2: Antimicrobial activity

Compd.	Diameter of zone of Inhibition (mm)			% Inhibition with reference to standard		
No.	*S. aureus* (100 µg/ml)	*E. coli* (100 µg/ml	*C. albicans*	*S. aureus*	*E.coli*	*C. albicans*
1	20	16	14	80	64	70
2	13	19	12	52	76	60
3	14	19	11	56	76	55
4	18	19	17	72	76	85
5	12	-	10	48	-	50
6	11	-	9	44	-	45
7	10	-	12	40	-	60
8	13	11	13	52	44	65
9	12	13	11	48	52	55
10	15	12	10	60	48	50
Ciprofloxacin	25	25	-	100	100	-
Ketoconazole	-	-	20	-	-	100

Antimicrobial activity

The synthesized compounds were screened for their antibacterial activity against Gram-positive S. aureus, Gram-negative E. *coli* strains and antifungal activity against C. *albicans* by cup plate method[12] (agar diffusion method). Ciprofloxacin and ketoconazole were used as standards. The test compounds and standards were evaluated at 100 µg/ml cone. Data is represented as zone of inhibition and % inhibition is calculated with reference to standards in Table 2.

RESULTS AND DISCUSSION

It has been observed that most of the compounds showed inhibition against *S. aureus, E. Coli* and *C. albicans.* Compounds (1 and 4) showed 80% and 72% inhibition respectively against s. *aureus* while as compounds (2, 3 and 4) showed 76% inhibition against *E. coli.* Compounds (1, 4 and 8) showed 70%, 85% and 65% inhibition respectively against *C. albicans.* The compound without substitution showed highest activity against *S. aureus.* Compounds with chlorine substitution showed highest activity against *E. coli.* The compound with H, Cl, and OCH_3 substitution showed highest activity against *C. albicans*.

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REFERENCES

1. Thomasco, M.L., Godwood, C.R., Weaver, A.E., Ochoada, M.J., Ford, W.C., Zurenko, E.G., Hamel, C.J., Stapert, D., Moerman, K.J., Schadt, D.R. and Yogi, H.B. "The synthesis and antibacterial activity of 1, 3, 4-thiadiazole phenyl oxazolidainone abnalogues". *Bioorg. Med. Chem. Lett.* **13**: 4193-4196 (2003).
2. Udupi, H.R. Rajeeva, B., Setty, R.S., Srinivasullu, N and Pasha, T.T. "Synthesis and biological activity of some 3, 5-disubstituted -6-thiono-s-triazolo [3, 4-b] (1, 3, 4)- thiadiazoles". *Ind. J. Heterocycl. Chem.* **13**: 229-232 (2004).
3. Joshi, S.H. and Thaker, M.K. Synthesis and pharmacological evaluation of 2-(3',5'-dichlorobenzo [b] thiophen-2'-yl)-5-arylamino-1, 3,4-thiadiazoles". *Ind. J. Chem.* **44**B: 410-412 (2005).
4. Terzioglu, N and Gursoy, A. "Synthesis and anticancer evaluation of some new hydrazone derivatives of 2, 6-dimethylimidazo [2, 1-b]-[1, 3, 4] thiadiazole-5-carbohydrazide". *Eur. J. Med. Chem.* **23**: 385-389 (1988).
5. Yadav, S.L., Zaidi, H.G. and Singh, N.B. "Synthesis and anifungal evaluation of some 1, 3, 4-thiadiazoles against P. oryzae and R. solani'. *Asian. J. Chem.* **15**: 1805-1807 (2003).
6. Yadav S.D.L. and Singh, S. "Synthesis of antiviral acyclic C-nucleosides incorporating thiazolo-1, 3, 4-oxa (thia) diazole or thiazolo-1, 2, 4-thiazolde structure as a nucleobase". *Ind. J. Chem.* **40**B: 440-442 (2001).
7. Siddiqui, N., Arshad, M.F., Khan, S.A. and Ahsan, W. "Synthesis, anticonvulsant, and neurotoxicity screening of 1-(substituted phenyl)-3-[5-substitited phenyl-1, 3, 4-thiadiazol-2yl]-2-thioxodihydropyrimidine-4, 6-(1H, 5h)-diones." *J. Pharm. Res.* **7**(2): 122-125 (2008).
8. Siddiqui, N., Ali, S., Khan, S.A., Drabu, S., Rana, A and Alam, A. "Synthesis of 3-arylamino-4aryl-5- (N-arylthiocarbonylimino)-4, 5-dihydro-1, 2, 4-thiadiazoles as anticonvulsant agents." *Ind. J. Heterocycl. Chem.* **14**(2): 159-160 (2004)
9. Siddiqui, N., Drabu, S, and Ali, S. "Biological significance of 1, 2, 4-thiadiazoles." *J. Sci. Phjarm.,* **2**(1): 33-38 (200).
10. Siddiui, N. "Synthesis and anticonvulsant activity of 2-(alkylcarbothioamido) hydrazine-5-ary-1, 3, 4-thiadiazole." *Him. Chem. Pharm. Bull,* **17**: 16-18 (2000).
11. Zhang, Z.Y., Sun, X.W., and Liang, H.T. "Synthesis and antibacterial activity of 4-aryl-1-(1-p-chlorophenyl-5-methyl-1, 2, 3-triazol-4-carbonyl) thiosemicarbazides and their related heterocyclic derivatives". *Ind. J. Chem.* **38**B: 679-683 (1999).
12. Barry, A.L. "The Antimicrobial Susceptibility Test: Principal and Pratices," edited by Illus Lea and Febiger, Philadelphia, U.S.A. 180 (1976).