International Journal of Pharmaceutical Chemistry

ISSN: 2249-734X (Online)
Journal DOI:10.7439/ijpc
CODEN:IJPCI4 (American Chemical Society)

Research Article

Synthesis, antimicrobial and QSAR studies of some new thiadiazepine derivatives

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Abstract

A new series of thiadiazepine derivatives **3a-l** were synthesized from base catalysed reaction between chalcones and triazoles. They were characterized by advanced spectral techniques like IR, ^{1}HNMR and mass spectroscopy and their antimicrobial studies were carried out. **3i** exhibited excellent activity against gram +ve bacteria. **3g** displayed significant antifungal activity. The logarithm of zone of inhibition of microorganisms were used for studying the quantitative structure activity relationships (QSAR) of the newly synthesized thiadiazepines and were carried out using Easy QSAR 1.0 by simple linear regression analysis. PaDEL Descriptor 2.13 predicted Eccentric connectivity index (ECCEN) and Chi path to be the best correlated QSAR model for antibacterial and anti-fungal activity of thiadiazepines against *Staphylococcus aureus* and *Asper gillusniger* respectively. The development of the best QSAR model for antimicrobial activity for thiadiazepines was confirmed by the high correlation between the observed and the predicted Log ZOI values.

Keywords: Thiadiazepine, Antimicrobial and QSAR

1. Introduction

Currently, there is a wide range and spectrum of effective antimicrobials. However the emerging problem of multidrug resistance is proving to be a bigger challenge than the infections themselves in the pre-antibiotic era. Antimicrobial resistance is a growing threat worldwide. Resistance mechanisms have been found for every class of antimicrobial agents and the search for new antimicrobials effective against various multiresistant strains is probably one of the most difficult challenges of medicinal chemistry. Development of new classes of antimicrobials is essential for the future.

1,2,4-Triazole, a five member heterocyclic with three nitrogen atoms in the ring which are by far the best-known class of triazoles, comprises wide variety of medicinal activities like antifungal, antimicrobial, anti-inflammatory, hypoglycemic, antidepressant, antitubercular, analgesic, anticancer and anticonvulsant[1-8]. Some of the marketed formulations which contain triazole ring are Terconozole, Itraconazole, Fluconazole, Bittertanol (fungicides), Trazodone (antidepressant) and Triazolam (sedative and hypnotic). 1,2,4-Triazole is an important emerging moiety in pharmaceutical study and a lot of work can be carried out on this molecule for obtaining better therapeutic activity.The synthesis of compounds belonging to thiadiazepine series constitute an important research area due to their interesting diverse biological activities such as antibacterial, antifungal, antiHIV, analgesic, anticoagulant, and antidepressant properties[9-16].

Structural requirements for a molecule to show any biological activity is defined by structure activity relationship studies. QSAR studies are relevant as the biological activity of a molecule is dependent on its physicochemical properties. Prompted by these observations and in continuation of our research work on nitrogen and sulphur containing biologically active molecules, we report the synthesis and QSAR analysis of some new triazolo-thiadiazepines.

2. Materials and methods

2.1 Chemistry

3-Substituted-4-amino-5-mercapto-1,2,4-triazoles **1a-b** were synthesized through multistep sequential reaction from different substituted phenols[17]. The condensation of substituted aromatic aldehydes with 4-substitutedacetophenone yielded six chalcones[18] **2a-f**. The reaction between triazoles **1a-b** and chalcones **2a-f** gave the twelve new thiadiazepines[19] **3a-l** (Scheme-1).

The chemicals used for this study were obtained from Merck and Aldrich Chemicals. Thin layer chromatography was conducted using 1:1 mixture of ethyl acetate and hexane solution for chalcones and 1:4 mixture of ethyl acetate and benzene for thiadiazepines as eluents to check their purity. The IR spectra were recorded in a Schimadzu FTIR 8400S spectrophotometer using KBr pellets. ^{1}H-NMR spectra were recorded in deuterated dimethyl sulphoxide in an AV500 NMR spectrometer with tetramethylsilane as internal standard. The mass spectra were recorded in a Schimadzu GCMS-QP5050 mass spectrometer. The elemental analysis of all compounds done in Flash thermo 1112 series CHN analyser gave the values within the permissible limit of 0.4 %. Melting points were determined by open capillary method and are uncorrected.

The IR, ^{1}HNMR and MS were consistent with the assigned structures. IR spectra of condensed thiadiazepines displayed disappearance of band at 1665 cm^{-1} due to C=O *str*. of chalcone and at 2750 cm^{-1} due to –SH *str*. of 5-substituted-4-amino-3-mercapto-1,2,4-triazoles. ^{1}H-NMR spectra of thiadiazepines showed the >CH-S proton at 5 ppm and –CH= proton at 7.5 ppm. The proton attached to nitrogen of thiadiazepine ring was observed at 8.5 ppm. The solvent peak due to DMSO-d_6 was observed at 2.4 ppm.

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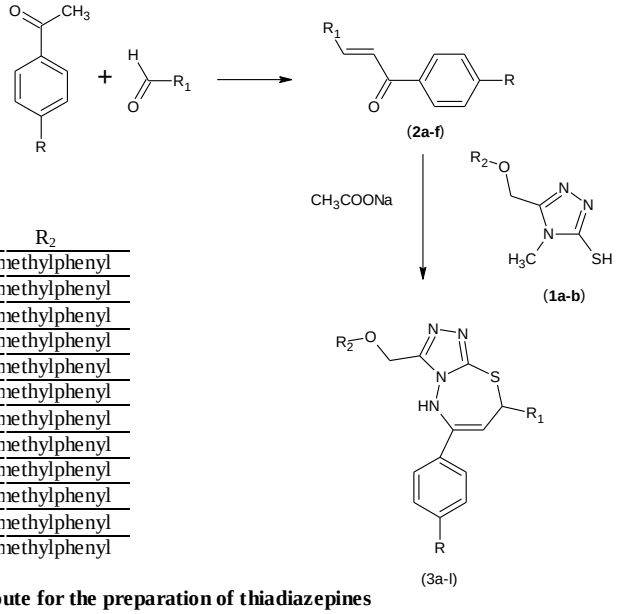


Comp. No.	R	R_1	R_2
3a	Fluoro	4-dimethoxy aminophenyl	2-methylphenyl
3b	Fluoro	4-dimethoxy aminophenyl	4-methylphenyl
3c	Chloro	4-dimethoxy aminophenyl	2-methylphenyl
3d	Chloro	4-dimethoxy aminophenyl	4-methylphenyl
3e	4-methoxy	4-dimethoxy aminophenyl	2-methylphenyl
3f	4-methoxy	4-dimethoxy aminophenyl	4-methylphenyl
3g	Fluoro	2,4-dimethoxyphenyl	2-methylphenyl
3h	Fluoro	2,4-dimethoxyphenyl	4-methylphenyl
3i	Chloro	2,4-dimethoxyphenyl	2-methylphenyl
3j	Chloro	2,4-dimethoxyphenyl	4-methylphenyl
3k	4-methoxy	2,4-dimethoxyphenyl	2-methylphenyl
3l	4-methoxy	2,4-dimethoxyphenyl	4-methylphenyl

Scheme-1: Synthetic route for the preparation of thiadiazepines

*General method for the preparation of 3-[(substituted)methyl]-6-(4-(substituted)phenyl)-8-[(substituted)phenyl)-5,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4] thiadiazepines***3a-l**

1 mmol of triazole**1a-b** and 1 mmol of chalcone **2a-f** dissolved in 15 mL of DMSO was refluxed for 10 h on a water bath in presence of sodium acetate. The reaction mixture was kept aside overnight and the solid separated was collected, washed, dried and recrystallized from ethanol.

*3-[(2-methylphenoxy)methyl]-6-(4-fluorophenyl)-8-(4-dimethylaminophenyl)-5,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines***(3a)**

Yellow solid (87 %); mp 116-118 °C; ir (KBr): 3034 (Ar. C-H *str*.), 2923, 2845 (methyl C-H *str*.), 1583 (Ar. C=C *str*.), 1308 (C-N *str*.), 1238 (C-O-C *asym. str*.), 1035 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.81 (6H, $N(CH_3)_2$), 2.42 (3H, $Ar.CH_3$), 5.03 (d, >CH-S of thiadiazepine ring), 5.48 (s, 2H, OCH_2), 7.59 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 12H, Ar.H), 8.55 (1H, thiadiazepine N-H) ppm; ms (m/z): 487 (M^+); *Anal*. calcd. for $C_{27}H_{26}FN_5OS$: C, 66.53; H, 5.34; N, 14.37. Found: C, 66.67; H, 5.36; N, 14.41.

*3-[(4-methylphenoxy)methyl]-6-(4-fluorophenyl)-8-(4-dimethylaminophenyl)-5,8-dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines***(3b)**

Yellow solid (77 %); mp 126-128 °C; ir (KBr): 3036 (Ar. C-H *str*.), 2924, 2842 (methyl C-H *str*.), 1581 (Ar. C=C *str*.), 1309 (C-N *str*.), 1240 (C-O-C *asym. str*.), 1036 (C-O-C *sym. str*.) cm^{-1} ; ^1H nmr (DMSO-d_6) δ: 2.81 (6H, $N(CH_3)_2$), 2.41 (3H, $Ar.CH_3$), 5.03 (d, >CH-S of thiadiazepine ring), 5.49 (s, 2H, OCH_2), 7.60 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 12H, Ar.H), 8.55 (1H, thiadiazepine N-H) ppm; ms (m/z): 487 (M^+); *Anal*. calcd. for $C_{27}H_{26}FN_5OS$: C, 66.53; H, 5.34; N, 14.37. Found: C, 66.71; H, 5.36; N, 14.43.

*3-[(2-methylphenoxy)methyl]-6-(4-chlorophenyl)-8-(4-dimethylaminophenyl)-5,8-dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines***(3c)**

Yellow solid (85 %); mp 122-124 °C; ir (KBr): 3035 (Ar. C-H *str*.), 2929, 2845 (methyl C-H *str*.), 1585 (Ar. C=C *str*.), 1310 (C-N *str*.), 1240 (C-O-C *asym. str*.), 1038 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.82 (6H, $N(CH_3)_2$), 2.42 (3H, $Ar.CH_3$), 5.03 (d, >CH-S of thiadiazepine ring), 5.48 (s, 2H, OCH_2), 7.59 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 12H, Ar.H), 8.54 (1H, thiadiazepine N-H) ppm; ms (m/z): 503 (M^+); *Anal*. calcd. for $C_{27}H_{26}ClN_5OS$: C, 64.41; H, 5.17; N, 13.92. Found: C, 64.61; H, 5.19; N, 13.97.

*3-[(4-methylphenoxy)methyl]-6-(4-chlorophenyl)-8-(4-dimethylaminophenyl)-5,8-dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines***(3d)**

Yellow solid (78 %); mp 128-130 °C; ir (KBr): 3037 (Ar. C-H *str*.), 2924, 2845 (methyl C-H *str*.), 1580 (Ar. C=C *str*.), 1308 (C-N *str*.), 1238 (C-O-C *asym. str*.), 1035 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.81 (6H, $N(CH_3)_2$), 2.41 (3H, $Ar.CH_3$), 5.03 (d, >CH-S of thiadiazepine ring), 5.49 (s, 2H, OCH_2), 7.60 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 12H, Ar.H), 8.55 (1H, thiadiazepine N-H) ppm; ms (m/z): 503 (M^+); *Anal*. calcd. for $C_{27}H_{26}ClN_5OS$: C, 64.41; H, 5.17; N, 13.92. Found: C, 64.56; H, 5.19; N, 14.96.

*3-[(2-methylphenoxy)methyl]-6-(4-anisyl)-8-(4-dimethylaminophenyl)-5,8-dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines***(3e)**

Yellow solid (84 %); mp 126-128 °C; ir (KBr): 3040 (Ar. C-H *str*.), 2930, 2850 (methyl C-H *str*.), 1585 (Ar. C=C *str*.), 1310 (C-N *str*.), 1240 (C-O-C *asym. str*.), 1038 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.82 (6H, $N(CH_3)_2$), 2.41 (3H, $Ar.CH_3$), 3.44 (3H, OCH_3), 5.04 (d, >CH-S of thiadiazepine ring), 5.47 (s, 2H, OCH_2), 7.59 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 12H, Ar.H), 8.56 (1H, thiadiazepine N-H) ppm; ms (m/z): 499 (M^+); *Anal*. calcd. for $C_{28}H_{29}N_5O_2S$: C, 67.33; H, 5.81; N, 14.03. Found: C, 67.47; H, 5.82; N, 14.06.

*3-[(4-methylphenoxy)methyl]-6-(4-anisyl)-8-(4-dimethylaminophenyl)-5,8-dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines***(3f)**

Yellow solid (67 %); mp 136-138 °C; ir (KBr): 3042 (Ar. C-H *str*.), 2927, 2850 (methyl C-H *str*.), 1580 (Ar. C=C *str*.), 1310 (C-N *str*.), 1235 (C-O-C *asym. str*.), 1040 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.82 (6H, $N(CH_3)_2$), 2.41 (3H, $Ar.CH_3$), 3.43 (3H, OCH_3), 5.04 (d, >CH-S of thiadiazepine ring), 5.47 (s, 2H, OCH_2), 7.59 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 12H, Ar.H), 8.55 (1H, thiadiazepine N-H) ppm; ms (m/z): 499 (M^+); *Anal*. calcd. for $C_{28}H_{29}N_5O_2S$: C, 67.33; H, 5.81; N, 14.03. Found: C, 67.42; H, 5.83; N, 14.06.

*3-[(2-methylphenoxy)methyl]-6-(4-fluorophenyl)-8-(2,4-dimethoxyphenyl)-5,8-dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine***(3g)**

Yellow solid (68 %); mp 126-128 °C; ir (KBr): 3038 (Ar. C-H *str*.), 2930, 2845 (methyl C-H *str*.), 1582 (Ar. C=C *str*.), 1308 (C-N *str*.), 1240 (C-O-C *asym. str*.), 1032 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.42 (3H, $Ar.CH_3$), 3.4 (6H, OCH_3), 5.03 (d, >CH-S of thiadiazepine ring), 5.47 (s, 2H, OCH_2), 7.58 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 11H, Ar.H), 8.55 (1H, thiadiazepine N-H) ppm; ms (m/z): 504 (M^+); *Anal*. calcd. for $C_{27}H_{25}FN_4O_3S$: C, 64.29; H, 4.96; N, 11.11. Found: C, 64.47; H, 4.97; N, 11.14.

*3-[(4-methylphenoxy)methyl]-6-(4-fluorophenyl)-8-(2,4-dimethoxyphenyl)-5,8-dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine***(3h)**
Yellow solid (71 %); mp 116-118 °C; ir (KBr): 3035 (Ar. C-H *str*.), 2925, 2840 (methyl C-H *str*.), 1583 (Ar. C=C *str*.), 1309 (C-N *str*.), 1238 (C-O-C *asym. str*.), 1028 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.42 (3H, Ar.CH_3), 3.4 (6H, OCH_3), 5.03 (d, >CH-S of thiadiazepine ring), 5.48 (s, 2H, OCH_2), 7.59 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 11H, Ar.H), 8.54 (1H, thiadiazepine N-H) ppm; ms (m/z): 504 (M^+); *Anal*. calcd. for $C_{27}H_{25}FN_4O_3S$: C, 64.29; H, 4.96; N, 11.11. Found: C, 64.35; H, 4.97; N, 11.13.

*3-[(2-methylphenoxy)methyl]-6-(4-chlorophenyl)-8-(2,4-dimethoxyphenyl)-5,8-dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine***(3i)**
Yellow solid (84 %); mp 136-138 °C; ir (KBr): 3038 (Ar. C-H *str*.), 2930, 2845 (methyl C-H *str*.), 1585 (Ar. C=C *str*.), 1312 (C-N *str*.), 1240 (C-O-C *asym. str*.), 1035 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.42 (3H, Ar.CH_3), 3.4 (6H, OCH_3), 5.03 (d, >CH-S of thiadiazepine ring), 5.48 (s, 2H, OCH_2), 7.59 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 11H, Ar.H), 8.55 (1H, thiadiazepine N-H) ppm; ms (m/z): 520 (M^+); *Anal*. calcd. for $C_{27}H_{25}ClN_4O_3S$: C, 62.31; H, 4.81; N, 10.80. Found: C, 62.45; H, 4.83; N, 10.84.

*3-[(4-methylphenoxy)methyl]-6-(4-chlorophenyl)-8-(2,4-dimethoxyphenyl)-5,8-dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines***(3j)**
Yellow solid (77 %); mp 130-132 °C; ir (KBr): 3037 (Ar. C-H *str*.), 2923, 2844 (methyl C-H *str*.), 1580 (Ar. C=C *str*.), 1310 (C-N *str*.), 1240 (C-O-C *asym. str*.), 1026 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.42 (3H, Ar.CH_3), 3.4 (6H, OCH_3), 5.03 (d, >CH-S of thiadiazepine ring), 5.48 (s, 2H, OCH_2), 7.59 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 11H, Ar.H), 8.55 (1H, thiadiazepine N-H) ppm; ms (m/z): 520 (M^+); *Anal*. calcd. for $C_{27}H_{25}ClN_4O_3S$: C, 62.31; H, 4.81; N, 10.80. Found: C, 62.43; H, 4.84; N, 10.84.

*3-[(2-methylphenoxy)methyl]-6-(4-anisyl)-8-(2,4-dimethoxyphenyl)-5,8-dihydro[1,2,4] triazolo[3,4-b][1,3,4]thiadiazepines***(3k)**
Yellow solid (67 %); mp 124-126 °C; ir (KBr): 3040 (Ar. C-H *str*.), 2925, 2840 (methyl C-H *str*.), 1585 (Ar. C=C *str*.), 1312 (C-N *str*.), 1240 (C-O-C *asym. str*.), 1028 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.42 (3H, Ar.CH_3), 3.4 (9H, OCH_3), 5.03 (d, >CH-S of thiadiazepine ring), 5.48 (s, 2H, OCH_2), 7.59 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 11H, Ar.H), 8.55 (1H, thiadiazepine N-H) ppm; ms (m/z): 516 (M^+); *Anal*. calcd. for $C_{28}H_{28}N_4O_4S$: C, 65.11; H, 5.43; N, 10.85. Found: C, 65.19; H, 5.44; N, 10.89.

*3-[(4-methylphenoxy)methyl]-6-(4-anisyl)-8-(2,4-dimethoxyphenyl)-5,8-dihydro[1,2,4] triazolo[3,4-b][1,3,4]thiadiazepines***(3l)**
Yellow solid (84 %); mp 132-134 °C; ir (KBr): 3038 (Ar. C-H *str*.), 2928, 2845 (methyl C-H *str*.), 1580 (Ar. C=C *str*.), 1310 (C-N *str*.), 1240 (C-O-C *asym. str*.), 1025 (C-O-C *sym. str*.) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.42 (3H, Ar.CH_3), 3.4 (9H, OCH_3), 5.03 (d, >CH-S of thiadiazepine ring), 5.48 (s, 2H, OCH_2), 7.59 (d, –CH= of thiadiazepine ring), 7.0-8.2 (m, 11H, Ar.H), 8.55 (1H, thiadiazepine N-H) ppm; ms (m/z): 516 (M^+); *Anal*. calcd. for $C_{28}H_{28}N_4O_4S$: C, 65.11; H, 5.43; N, 10.85. Found: C, 65.23; H, 5.43; N, 10.88.

2.2 Pharmacology

Disc Diffusion Method (Kirby-Bauer Method)[20] was employed to assess the antimicrobial potential of thiadiazepines. The efficacy of thiadiazepines as antimicrobial agents was studied against gram-positive bacteria *S. aureus*, gram-negative bacteria *E. coli* and fungi *A. niger*. Thiadiazepines were dissolved in DMSO to make a concentration of 10 µg/mL. DMSO, used as control showed no antibacterial activity. The petri plates were initially plated with nutrient agar media, dipped in prepared thiadiazepine solution, placed in swab cultured inoculated plates using sterile forceps, gently pressed and were incubated at 37 °C for 24 h for antimicrobial and for a week for antifungal studies. Tetracycline and Ketaconazole were used as standard antibacterial and antifungal drugs respectively. The average diameters of inhibition zones of microbial growth around the discs were recorded.

2.3 QSAR studies

The molecules were converted from 2D to 3D structures to perform the QSAR studies. The descriptors for thiadiazepines were predicted using PaDEL software[21]. Easy QSAR 1.0 was employed for simple linear regression analysis to study the correlation between the Log ZOI values of thiadiazepines and the physicochemical descriptors. Various statistical parameters like the square of the correlation coefficient (r^2), the Fischer's value of significance (F) and the standard error of estimate (s)was used to choose the most agreeing QSAR model[22] and the correlation between the experimental and predicted antimicrobial activity was studied using Easy QSAR tool.

3. Results and discussion

The results revealed that most of the compounds showed moderate antibacterial activity.**3i** with chloro and dimethoxy substituent exhibited relatively high inhibitory effect on *S. aureus*.Thiadiazepines**3c** and **3d** displayed high sensitivity against *E.coli*. Compound **3g** which had fluoro and dimethoxy substituents in the phenyl ring demonstrated the best antifungal activity by inhibiting spore germination of *A. niger*. The structure-antimicrobial activity relationship of the synthesized compounds revealed that the compounds with halogen substituents exhibited maximum antimicrobial activity. This can be attributed to the increased dipole moment in C-X bond which might have enhanced the intermolecular interactions and hydrogen bonding leading to high antimicrobial potency of the molecule.

The observed and the predicted Log ZOI of thiadiazepines are listed in Table 1and the correlation between them is depicted in Fig.1 and Fig.2 respectively.

Table 1: Results of antimicrobial studies of thiadiazepines

Compound No.	*S. aureus*			*A. niger*		
	ZOI (mm)	Observed Log ZOI	Predicted Log ZOI	ZOI (mm)	Observed Log ZOI	Predicted Log ZOI
3a	11	2.398	2.87	0	0	-
3b	07	1.946	2.21	07	1.946	2.24
3c	19	2.944	2.94	12	2.485	2.65
3d	0	0	-	0	0	-
3e	10	2.303	2.43	08	2.079	1.98
3f	06	1.792	1.77	05	1.609	1.57
3g	14	2.639	2.60	23	3.135	2.65
3h	0	0	-	10	2.303	2.24
3i	25	3.219	2.60	13	2.565	2.65
3j	07	1.946	1.90	07	1.946	2.24
3k	10	2.303	2.15	08	2.079	1.98
3l	04	1.386	1.47	05	1.609	1.57

Fig 1: Observed and predicted antibacterial activity correlation for thiadiazepines using the best QSAR model

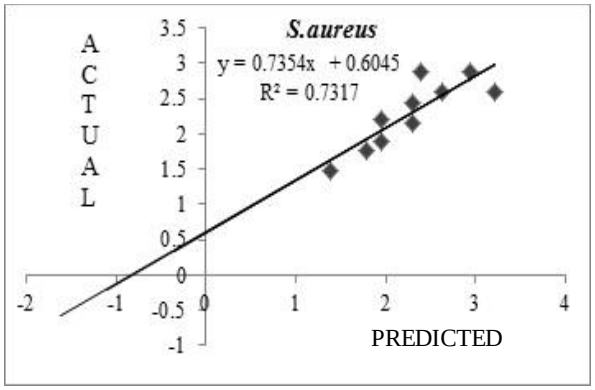
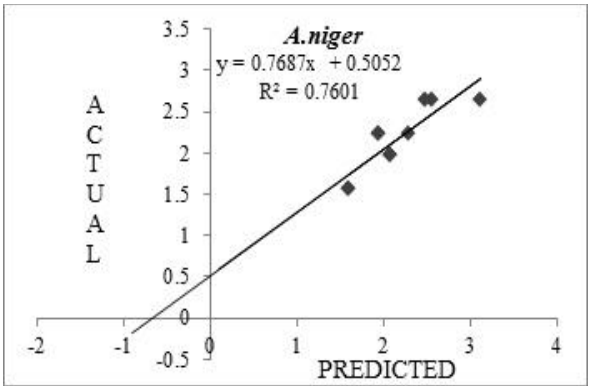


Fig 2: Observed and predicted antifungal activity correlation for thiadiazepines using the best QSAR model



In the QSAR model developed by the simple linear regression analysis, the highest value of the square of the correlation coefficient (r^2 = 0.73), and the suitable values of F and s (21.77and 0.73, respectively), were obtained when Log ZOI (antibacterial activity) of thiadiazepines against *S. aureus* at 100 µg/mL, was correlated with the ECCEN to identify the descriptor contribution as presented in equation 1. ECCEN is a distance based molecular structure descriptor and has been shown to give a high degree of predictability of pharmaceutical compounds. It provides leads to the development of safe and potent bioactive compounds. The lower the value of ECCEN, the higher would be the activity of thiadiazepines against *S. aureus* as indicated by its negative sign.

Y=1.491281047831E+001 + -1.307363619996E-002*(X1) …… (1)

n = 10, r^2 = 0.73, F = 21.77, s = 0.73

The Log ZOI (antifungal activity) of thiadiazepines, against *A.niger* at 100 µg/mL, was correlated with SP-2 and the results are depicted in equation 2.

Y= 6.376460445335E+001 + -3.936232578050E+000*(x1)…….. (2)

n = 10, r^2 = 0.76, F = 25.29, s = 0.47

The negative sign of parameter, SP-2, indicated the inverse relationship between the SP-2 value and the antifungal activity of thiadiazepines against *A. niger*. No statistically significant results for inhibitory activity of thiadiazepines against *E. coli* were obtained using PaDEL descriptors.

4. Conclusion

Twelve new thiadiazepines synthesized by the reaction between chalcones and triazoles were subjected to antimicrobial studies. Compound **3i** and **3g** was identified as the most potent within this study with a promising antibacterial and antifungal potential against *S.aureus* and *A. niger*. The parameters, ECCEN and SP-2, were remarkably related to the antibacterial and anti-fungal activities of thiadiazepines against *S. aureus* and *A. niger* at 100 µg/mL. The development of the best QSAR model was suggested by the correlation between the observed and the predicted Log ZOI values for thiadiazepines. The potential of thiadiazepines**3i** and **3g** should be further explored for development of antimicrobial agents.

References

1. Dobrowsky W, Huigol NG, Jayatilake S, Kizilbash NI, OkkanS, Kagiya TV, *et al*.AK-2123 (Sanazol) as a radiation sensitizer in the treatment of stage III cancer cervix: initial results of an IAEA multicentre randomized trial. *J Cancer Res Ther* 2005; 1(2): 75-8.
2. Padmavathi V, Reddy GS, Padmaja A, Kondaiah P, Ali-Shazia. Synthesis, antimicrobial and cytotoxic activities of 1,3,4-thiadiazoles and 1,2,4-triazoles. *Eur J Med Chem* 2009; 44: 2106-12.
3. Hafez HN, Abdel-RahmanBAE. Synthesis and antitumor activity of substituted triazolo[4,3-α]pyrimidin-6-sulfonamide with an incorporated thiazolidinone moiety. *Bioorg Med Chem Lett* 2009; 19: 4143-47.
4. Neha S, Sharma PK, Rupesh D, Nitin, K. Recent advancement of triazole derivatives and their biological significance. *J Chem Pharm Res*2011; 3(2):126-33.
5. Nadeem S, Waquar A, Shamsher A M, Ruhi A, Sanjay J, Bishmillah A, *et al*. Triazoles: as potential bioactive agents. *Intl J Pharm Sci Rev Res* 2011; 8: 161-9.
6. Patel K D, Mistry B D, Desai, KR. Synthesis and antimicrobial activity of 1,2,4-triazoles. *J Indian Chem Soc* 2002; 79: 964-65.
7. Prasad A R, Rao A N, Ramalingan T, Sattur, PB. Synthesis and biological Activity 4-amino-3-aryloxyalkyl-5-mercepto-1,2,4-triazoles. *Indian Drugs* 1988; 25(7): 301-4.
8. Swamy SN, Basappa, Priya BS, Prabhuswamy B, Doreswamy B H, Prasad S, *et al*. Synthesis of pharmaceutically important condensed heterocyclic 4,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives as antimicrobials. *Eur J Med Chem* 2006; 41: 531-38.
9. Anshu D, Ruby S, Sarita, K. Microwave enhanced solid support synthesis of fluorine containing benzopyrano-triazolo-thiadiazepines as potent antifungal agents. *Bioorg Med Chem* 2006; 14: 1303-8.
10. Kidwai M, Sapra P, Misra P, Saxena RK, Singh, M. Microwave assisted solid support synthesis of novel 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepines as potent antimicrobial agents. *Bioorg MedChem* 2001; 9: 217-20.
11. Gururaja R, Jyoti C H, Vagdevi H M, Kalluraya B. A facile synthesis of quinolino-thiadiazepines and their biological activity. *Indian J HetChem* 2004; 14: 97-100.
12. Kalluraya B, Nayak J, Vagdevi H M. One pot synthesis of 3-arylaminomethyl]-9/11 substituted-1,2,4-triazolo[3,4-b][1,3,4]-quinolinothiadiazepines. *Indian J Het Chem* 2005; 14: 257-58.
13. Kalluraya B, Vishwanatha P, Jyothi C H, Priya V F, Rai G. Sydnone derivatives: part-V1: synthesis of some triazolothiadiazepines and their biological activity. *Indian J Het Chem* 2003; 12: 355-56.

14. Geetha A S, Vijayaraj R, Kumar T R, Anand R S. Synthesis of certain 3-pyridyl [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine and evaluation of their possible biological activities. *Int J Res Pharm Biomed Sci* 2011; 2: 155-9.
15. Monica G, Satya P, Rajive G. Microwave assisted one pot synthesis of antifungal active 1-substituted-3,7-dialkyl/aryl-4H-pyrazolo[4,5-f][1,2,4]triazolo[3,4-b][1,3,4] thiadiazepine. *Indian J Het Chem* 2009; 48B: 460-66.
16. Dandia A, Singh R, Khaturia S. Microwave enhanced solid support synthesis of fluorine containingbenzopyrano-triazolo-thiadiazepines as potent anti-fungal agents. *Bioorg Med Chem* 2006; 14: 1303-8.
17. Isloor A M, Kalluraya B, Shetty P. Regioselective reaction: Synthesis, characterization and pharmacological studies of some new mannich bases derived from 1,2,4-triazoles. *Eur J Med Chem* 2009; 44: 3784-7.
18. Babasaheb P B, Shrikant S G, Ragini G B, Jalinder V T,Chandrahas NK. Synthesis and biological evaluation of simple methoxylated chalcones as anticancer, anti-inflammatory and antioxidant agents. *Bioorg Med Chem*2010; 18: 1364-70.
19. Om P, Deepak S,Ravi K. A facile synthesis of new 7,8-dihydro-s-triazolo-3-alkyl-6,8-diaryl[3,4-b][1,3,4]thiadiazepines. *Indian J HeterocyclChem*2004;14: 111-4.
20. Jorgensen JH,TumidgeJD. Susceptibility test methods dilution and disc diffusion methods in Manual Clinical Microbial: Washington DC,2007,1152-72.
21. Naruka S G, Mahajan S S. Conventional and microwave assisted synthesis and QSAR studies of coumarinyl chalcones as potent antimicrobial agents *Intl J Res PharmChem*2011;1(4): 879-90.
22. Yap C W. PaDEL-descriptor: an open source software to calculate molecular descriptors and fingerprints. *J Comput Chem* 2011; 32(7): 1466-74.