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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological evaluation of new [1,3,4]thiadiazepino[7,6-*b*]quinolin-2-amines as potent anti-microbial agents

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Abstract Four series of 56 new thiadiazepinoquinoline amines were synthesized and characterized by spectroscopic techniques (NMR, IR, and MS) and elemental analysis. All the compounds were screened for in vitro anti-microbial activity. Highest inhibitory activity (MIC of 0.03 mg/ml) was exerted by **2e** against *Bacillus subtilis* and *Streptococcus pyogenes*, **2f** against *Escherichia coli* and *Streptococcus pyogenes*, and **4k** against only *Bacillus subtilis*. Only compounds **1g** and **2g** revealed potent anti-fungal activity (MIC 0.03 mg/ml) compared to the standard against *Alternaria alternata*. Most of the compounds exhibited better anti-bacterial activity than anti-fungal activity against the microorganisms employed in this study. These studies suggest that the thiadiazepinoquinoline scaffold may serve as a new promising template for further elaboration as anti-bacterial and anti-fungal drugs.

Keywords 2-Chloro-3-formylquinoline · [1,3,4]Thiadiazepino[7,6-*b*]quinolin-2-amines · Thiosemicarbazides · Anti-microbials

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Introduction

Heterocyclic compounds are well known for their wide range of biological applications. Six- and seven-membered heterocycles occupy a unique position due to dominant pharmacological applications (Forest *et al*., 1992; Natalya *et al*., 2002). Quinolines and their derivatives, which represent a major class of heterocycles (Meth-Cohn and Narine, 1978), are widely found in natural products (Michael, 2003; Michael, 2004) and drugs (Alhaider *et al*., 1985; Campbell *et al*., 1988; Du, 2003) and exhibit significant role in medicinal chemistry. Several quinoline derivatives have been reported to possess bactericidal (Awad *et al*., 1991), anti-malarial (Ginsburg *et al*., 1999), anti-allergenic (Althuis *et al*., 1980) and anti-inflammatory (Dillard *et al*., 1973) properties. Some of the famous anti-malarial drugs, containing quinoline ring system, available in the market are plasmoquine (Manske and Kulka, 1953), primaquine, and chloroquine (Singh *et al*., 1978). Similarly, some quinoline derivatives are found to have anti-cancer and anti-tumor activities (Loaiza *et al*., 2004). Among the quinolines, 2-chloro-3-formylquinolines find an important place in synthetic organic chemistry, as these are key intermediates for further β-annelation of a wide variety of ring systems and for the inter-conversions of many functional groups (Meth-Cohn, 1993). Certain thiadiazepine analogs have displayed neuroprotection against neurodegenerative diseases such as Alzheimer's disease (Gonzalez-Munoz *et al*., 2010). Thiadiazepines show anti-microbial (Demirbas *et al*., 2005; Dandia *et al*., 2006; Reddy and Reddy, 2010), anti-viral (Farghalya *et al*., 2006), anthelmintic (Kritsanida *et al*., 2002), and anti-HIV activities (Artico *et al*., 1996).

In continuation of our on-going research on various biologically active quinoline derivatives (Rizvi *et al*.,

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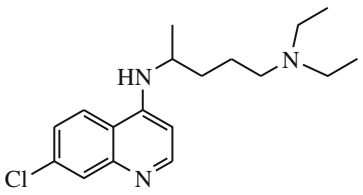
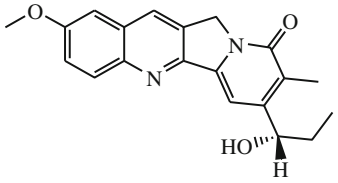
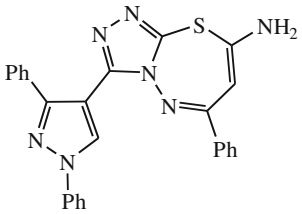


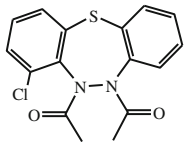
Chloroquine
(Antimalarial)



S-9-Methoxymappic ine
(Anti cancer and Anti HIV)



[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines
(Potent antiviral agent)



1,4,5-Dibenzo[*b*,*f*]thiadiazepine analogue
(exhibits neuroprotection against
neurodegenerative diseases)

Fig. 1 Structures of some quinoline- and thiadiazepine-based drugs

2010, 2012) and due to versatile anti-microbial activities of thiadiazepines, we herein report synthesis of four series of new (2*Z*,4*Z*)-9-chloro-10-methyl/8-methyl/10-methyl/8-methoxy-*N*-aryl/alkyl-[1,3,4]thiadiazepino[7,6-*b*]quinolin-2-amines (**1a**–**n**, **2a**–**n**, **3a**–**n**, and **4a**–**n**) with the perception that the synergism of quinoline and thiadiazepino nuclei would likely to possess significant biological activities (Fig. 1; Table 1).

Results and discussion

Chemistry

(2*Z*,4*Z*)-9-Chloro-10-methyl/8-methyl/10-methyl/8-methoxy-*N*-aryl/alkyl-[1,3,4]thiadiazepino[7,6-*b*]quinolin-2-amines (**1a**–**n**, **2a**–**n**, **3a**–**n**, and **4a**–**n**) were synthesized from commercially available four anilines following a three-step synthetic route. The latter were initially *N*-acetylated, using AcOH with H_3PO_4 or AcOH with Zn-dust under conventional as well as microwave conditions to get acetanilides in excellent yields (Redasani *et al*., 2010; Kwon *et al*., 1997; Brahmachari *et al*., 2010). 2-Chloro-3-formylquinoline, backbone, in turn was constructed by Meth-Cohn cyclization of acetanilides using conventional and microwave procedures (Meth-Cohn *et al*., 1981; Paul *et al*., 2000; Ajaypal and Chourasia, 2011). Finally, cyclocondensation of 2-chloro-3-formylquinolines was achieved by treating them with diverse thiosemicarbazides, following reported procedure (Raghavendra *et al*., 2006; Scheme 1).

All the condensation reactions were also attempted under microwaves and found more effective than in thermal conditions due to greater yield and lesser reaction time (Table 2). Thiadiazepine ring closure was proved to be more effective relative to reported procedure in terms of substitution pattern of tricyclic thiadiazepino quinoline skeleton, reaction kinetics, and yields (Table 2). The acceleration of ring closure may be attributed to greater stabilization of cyclized product through resonance (Fig. 2).

Structure of the synthesized compounds (**1a**–**n**, **2a**–**n**, **3a**–**n**, and **4a**-**n**) was confirmed on the basis of elemental analysis and spectral data (IR, ^{1}HNMR, and MS). IR spectra of all the compounds showed absorption bands in the regions 1,600–1,660 cm^{-1} corresponding to C=N stretching bands because of ring closure. Absorption bands at 3,401–3,492 cm^{-1} and 1,384 cm^{-1} were also observed due to NH and C–S, respectively.

In ^{1}H NMR spectra of all the compounds, NH proton was observed at δ 8.48–9.87 ppm, while H-5 appeared at δ 8.50–9.19 each as singlet. The possible explanation for H-5 being more shielded in compound **2j** compared to **2a** is the steric hindrance between the two methyl groups at C_2/C_6 in ring D and "S" atom in ring C which are in close proximity, pushes the former ring out of the plane (Figs. 2, 3).

In continuation of our endeavors, we have synthesized four series of 56 new compounds and evaluated their anti-bacterial

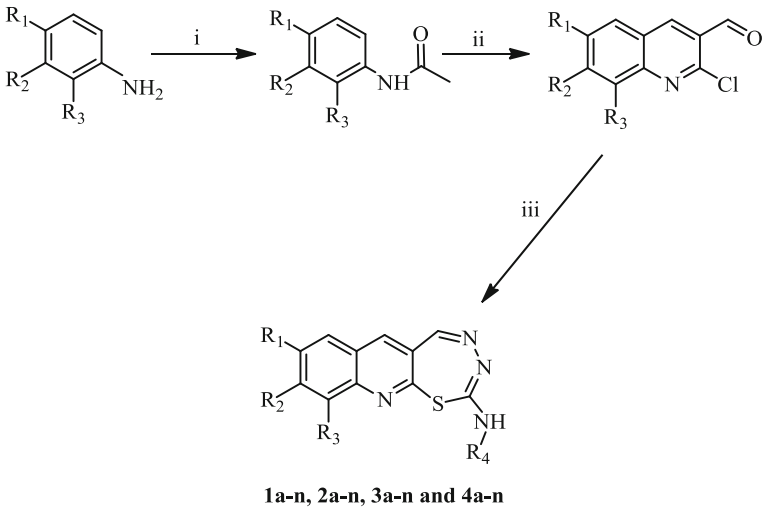
Table 1 Alkyl or aryl moiety in [1,3,4]thiadiazepino[7,6-*b*]quinolin-2-amines (**1a–n**), (**2a–n**), (**3a–n**), and (**4a–n**)

Compounds	R_1	R_2	R_3	R_4
1a	CH_3	H	H	Phenyl
1b	CH_3	H	H	2-Fluorophenyl
1c	CH_3	H	H	3-Fluorophenyl
1d	CH_3	H	H	4-Fluorophenyl
1e	CH_3	H	H	2-Chlorophenyl
1f	CH_3	H	H	3-Chlorophenyl
1g	CH_3	H	H	4-Chlorophenyl
1h	CH_3	H	H	*o*-Tolyl
1i	CH_3	H	H	*p*-Tolyl
1j	CH_3	H	H	2,6-Dimethylphenyl
1k	CH_3	H	H	2,4-Dimethylphenyl
1l	CH_3	H	H	4-Ethylphenyl
1m	CH_3	H	H	Benzyl
1n	CH_3	H	H	2-Morpholinoethyl
2a	OCH_3	H	H	Phenyl
2b	OCH_3	H	H	2-Fluorophenyl
2c	OCH_3	H	H	3-Fluorophenyl
2d	OCH_3	H	H	4-Fluorophenyl
2e	OCH_3	H	H	2-Chlorophenyl
2f	OCH_3	H	H	3-Chlorophenyl
2g	OCH_3	H	H	4-Chlorophenyl
2h	OCH_3	H	H	*o*-Tolyl
2i	OCH_3	H	H	*p*-Tolyl
2j	OCH_3	H	H	2,6-Dimethylphenyl
2k	OCH_3	H	H	2,4-Dimethylphenyl
2l	OCH_3	H	H	4-Ethylphenyl
2m	OCH_3	H	H	Benzyl
2n	OCH_3	H	H	2-Morpholinoethyl
3a	H	H	CH_3	Phenyl
3b	H	H	CH_3	2-Fluorophenyl
3c	H	H	CH_3	3-Fluorophenyl
3d	H	H	CH_3	4-Fluorophenyl
3e	H	H	CH_3	2-Chlorophenyl
3f	H	H	CH_3	3-Chlorophenyl
3g	H	H	CH_3	4-Chlorophenyl
3h	H	H	CH_3	*o*-Tolyl
3i	H	H	CH_3	*p*-Tolyl
3j	H	H	CH_3	2,6-Dimethylphenyl
3k	H	H	CH_3	2,4-Dimethylphenyl
3l	H	H	CH_3	4-Ethylphenyl
3m	H	H	CH_3	Benzyl
3n	H	H	CH_3	2-Morpholinoethyl
4a	H	Cl	CH_3	Phenyl
4b	H	Cl	CH_3	2-Fluorophenyl
4c	H	Cl	CH_3	3-Fluorophenyl
4d	H	Cl	CH_3	4-Fluorophenyl
4e	H	Cl	CH_3	2-Chlorophenyl
4f	H	Cl	CH_3	3-Chlorophenyl
4g	H	Cl	CH_3	4-Chlorophenyl
4h	H	Cl	CH_3	*o*-Tolyl
4i	H	Cl	CH_3	*p*-Tolyl
4j	H	Cl	CH_3	2,6-Dimethylphenyl
4k	H	Cl	CH_3	2,4-Dimethylphenyl
4l	H	Cl	CH_3	4-Ethylphenyl
4m	H	Cl	CH_3	Benzyl
4n	H	Cl	CH_3	2-Morpholinoethyl

activity against three Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, and *Streptococcus pyogenes*) and three Gram-negative bacteria (*Escherichia coli*, *Klebsiella aerogenes*, and *Salmonella typhimurium*) by determining their minimum inhibitory concentrations (MICs) using the agar dilution technique (Hanel and Raether, 1988) and chloramphenicol as reference drug. Chloramphenicol is considered a prototypical broad spectrum antibiotic and frequently found as a drug of choice in the third world and is effective against a wide variety of Gram-positive bacteria (including most strains of MRSA), Gram-negative bacteria, and anaerobes (Shakila *et al*., 2007). Due to resistance and safety concerns, it is no longer a first-line agent for any infection in developed nations, although it is sometimes used topically for eye infections. Nevertheless, the global problem of advancing bacterial resistance to newer drugs has led to renewed interest in its use (Falagas *et al*., 2008).

MICs of the active compounds against the susceptible pathogenic organisms are presented in Table 3. The anti-microbial spectrum of thiadiazepino[7,6-*b*]quinolin-2-amines against all strains demonstrated that all the compounds were the most active ones. Most of the compounds presented an MIC in the range of 0.03–0.50 mg/ml against all strains. An insight to the activities of different compounds obtained reveals that 11 compounds (**2c**, **2e**, **2f–g**, **4b–c**, **4g–h**, **4j–k**, **4m**) are more active against *B. subtilis* (Gram-positive bacterium, MIC 0.03–0.06 mg/ml). Likewise, compounds (**4a**, **4f**, and **4k**) exhibited more activity against *E. coli* (Gram-negative bacterium, MIC 0.06 mg/ml). By screening a large number of compounds, we were able to establish some general trends with respect to the structure–activity relationship, but it was not possible to draw clear and detailed relationships for any of the bioactivities. Higher activity of all the compounds generally against all the strains may be attributed to the presence of NH group flanked by rings C and D. Moreover, it seems that incorporation of either OMe/Cl in ring A or F/Cl in ring D regardless of their orientation enhances the anti-microbial activity.

Antifungal activity of the synthesized compounds was also elucidated against five strains of fungi, *Trichoderma*



1a-n, 2a-n, 3a-n and 4a-n

Scheme 1 Reaction protocol for the conversion of anilines to (2*Z*, 4*Z*)-9-chloro-10-methyl/8-methyl/10-methyl/8-methoxy-*N*-aryl/alkyl-[1,3,4]thiadiazepino[7,6-*b*]quinolin-2-amines. (*i*) AcOH, H_3PO4, reflux/microwaves or AcOH, Zn dust, reflux/microwaves, (*ii*) $POCl_3$, DMF, reflux/microwaves, and (*iii*) thiosemicarbazides, *p*-TsOH, DMF/EtOH, reflux/microwaves

reesei, *Aspergillus flavus*, *Alternaria alternata*, *Aspergillus niger*, and *Drechslera australiensis* by determining the MICs through microdilution technique (Espinel-Ingroff, 2001). Activity of each compound was compared with mancozeb as standard and the results are shown in Table 4. Twenty-one compounds (**1h**, **1j–k**, **1n**, **2b**, **2g**, **3h**, **3j–k**, **3n**, and **4a–k**) exhibited excellent activity (MIC 0.06–0.25 mg/ml) against *T. reesei*. Similarly, 13 compounds (**1g**, **2b**, **2d**, **2f–g**, **2k**, **4a**, **4d–e**, **4g–h**, and **4j–k**) also showed promising activity (0.030–0.25 mg/ml) against *A. alternata*.

Experimental

General

All the chemicals were purchased from E. Merck, Alpha Aesar or Fluka and used without purification. However, solvents were purified through distillation. ^{1}H NMR spectra were recorded on a Bruker/XWIN NMR (300 and 400 MHz). Chemical shifts are reported in ppm referenced to the residual solvent signal. FT-IR spectra were recorded on a Thermo Nicolet IR 200 spectrometer. Mass spectra were recorded on LTQXL (Thermo Fisher Scientific) instrument using CI mode. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Microwave-assisted reactions were carried out in a household MW oven (Oriente-NN-781JF) equipped with inverter technology (generating fixed frequency throughout the required time) for realistic control of the microwaves operating at multiples of 100 up to 1,000 W generating 2,450-MHz frequency. The apparatus was modified for laboratory applications, equipped with magnetic stirrer and an external reflux condenser. Elemental analysis was carried out using a Perkin Elmer 2400-CHN Analyzer.

General procedure for the synthesis of (2Z,4Z)-9-chloro-10-methyl/8-methyl/10-methyl/8-methoxy-N-aryl/alkyl-[1,3,4] thiadiazepino[7,6-b]quinolin-2-amines ***(1a–n, 2a–n, 3a–n, and 4a–n)***

First, four precursors, 7-chloro-8-methyl/6-methyl/8-methyl/6-methoxy-substituted 2-chloro-3-formyl quinolines, were synthesized according to the literature method (Meth-Cohn *et al*., 1981; Paul *et al*., 2000; Ajaypal and Chourasia, 2011). Cyclocondensation was achieved following reported procedure (Raghavendra *et al*., 2006). A mixture of substituted quinoline (0.5 mmol), thiosemicarbazide (0.5 mmol), catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH), and absolute EtOH (20 ml) was refluxed till completion of the reaction (for yields, reaction conditions, and reaction times, see Table 1). After completion of reaction (as indicated by TLC), the contents were poured over crushed ice, stirred well and filtered. Precipitates obtained were recrystallised from aqueous DMF to get pure compounds (**1a–n**, **2a–n**, **3a–n**, and **4a–n**).

Using microwaves A mixture of substituted quinoline (0.5 mmol) and thiosemicarbazide (0.5 mmol), catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) and anhydrous dimethylformamide (DMF) (15 ml) were added and contents were irradiated under microwave oven for 50–120 s at an interval of 20–30 s at 210 W (for yields, reaction conditions, and reaction times, see Table 1). After completion of the reaction (as indicated by TLC), the contents were poured over crushed ice, stirred well and filtered. Precipitates obtained were recrystallised from aqueous DMF to get the pure product (**1a–n**, **2a–n**, **3a–n**, and **4a–n**).

*(2Z,4Z)-8-Methyl-N-phenyl-[1,3,4]thiadiazepino[7,6-b] quinolin-2-amine (**1a**)* Yellow solid; m.p. 106 °C. IR (KBr) cm^{-1}: 3,466 (N–H), 1,660 (C=N), 1,549, 1,586

Table 2 Physical and analytical data (CHN analysis) of [1,3,4]thiadiazepino[7,6-*b*]quinolin-2-amines (**1a–n**), (**2a–n**), (**3a–n**), and (**4a–n**)

Compounds	Reaction conditions				Mol. formula	Analysis %		
	Conventional		Microwave (210 W)			Calculated (found)		
	Time (min)	Yield (%)	Time (s)	Yield (%)		C	H	N
1a	90	78	60	93	$C_{18}H_{14}N_4S$	67.90 (67.88)	4.43 (4.45)	17.60 (17.61)
1b	75	80	60	94	$C_{18}H_{13}FN_4S$	64.27 (67.29)	3.90 (3.88)	16.66 (16.59)
1c	70	79	60	93	$C_{18}H_{13}FN_4S$	64.27 (67.29)	3.90 (3.88)	16.66 (16.59)
1d	40	81	50	93	$C_{18}H_{13}FN_4S$	64.27 (67.29)	3.90 (3.88)	16.66 (16.59)
1e	55	76	50	82	$C_{18}H_{13}ClN_4S$	61.27 (67.30)	3.71 (3.69)	15.88 (15.88)
1f	50	82	60	88	$C_{18}H_{13}ClN_4S$	61.27 (67.30)	3.71 (3.69)	15.88 (15.80)
1g	45	85	60	94	$C_{18}H_{13}ClN_4S$	61.27 (67.30)	3.71 (3.69)	15.88 (15.80)
1h	40	78	90	82	$C_{19}H_{16}N_4S$	68.65 (68.67)	4.85 (4.84)	16.85 (16.84)
1i	35	83	120	88	$C_{19}H_{16}N_4S$	68.65 (68.67)	4.85 (4.84)	16.85 (16.84)
1j	55	72	60	83	$C_{20}H_{18}N_4S$	69.34 (69.32)	5.24 (5.25)	16.17 (16.17)
1k	50	77	50	94	$C_{20}H_{18}N_4S$	69.34 (69.32)	5.24 (5.25)	16.17 (16.18)
1l	45	81	60	93	$C_{20}H_{18}N_4S$	69.34 (69.37)	5.24 (5.22)	16.17 (16.18)
1m	50	84	50	88	$C_{19}H_{16}N_4S$	68.65 (68.67)	4.85 (4.84)	16.85 (16.84)
1n	35	78	50	89	$C_{18}H_{21}N_5OS$	60.82 (60.84)	5.95 (5.93)	19.70 (19.70)
2a	75	76	60	88	$C_{18}H_{14}N_4OS$	64.65 (64.64)	4.22 (4.24)	16.75 (16.75)
2b	80	79	60	94	$C_{18}H_{13}FN_4OS$	61.35 (61.37)	3.72 (3.70)	15.90 (15.91)
2c	60	81	60	94	$C_{18}H_{13}FN_4OS$	61.35 (61.38)	3.72 (3.70)	15.90 (15.90)
2d	30	83	90	94	$C_{18}H_{13}FN_4OS$	61.35 (61.36)	3.72 (3.71)	15.90 (15.91)
2e	45	72	60	83	$C_{18}H_{13}ClN_4OS$	58.61 (58.63)	3.55 (3.56)	15.19 (15.18)
2f	40	79	60	88	$C_{18}H_{13}ClN_4OS$	58.61 (58.60)	3.55 (3.56)	15.19 (15.18)
2g	40	80	50	94	$C_{18}H_{13}ClN_4OS$	58.61 (58.63)	3.55 (3.55)	15.19 (15.19)
2h	35	80	60	83	$C_{19}H_{16}N_4OS$	65.50 (65.53)	4.63 (4.65)	16.08 (16.09)
2i	40	81	120	84	$C_{19}H_{16}N_4OS$	65.50 (65.53)	4.63 (4.65)	16.08 (16.09)
2j	60	80	60	94	$C_{20}H_{18}N_4OS$	66.28 (66.31)	5.01 (5.00)	15.46 (15.48)
2k	45	82	60	89	$C_{20}H_{18}N_4OS$	66.28 (66.31)	5.01 (5.00)	15.46 (15.48)
2l	35	84	60	94	$C_{20}H_{18}N_4OS$	66.28 (66.30)	5.01 (5.02)	15.46 (15.48)
2m	50	81	60	85	$C_{19}H_{16}N_4OS$	65.50 (65.52)	4.63 (4.66)	16.08 (16.07)
2n	40	79	60	84	$C_{18}H_{21}N_5O_2S$	58.20 (58.17)	5.70 (5.72)	18.85 (18.84)
3a	60	72	70	91	$C_{18}H_{14}N_4S$	67.90 (67.87)	4.43 (4.45)	17.60 (17.61)
3b	40	80	90	90	$C_{18}H_{13}FN_4S$	64.27 (67.29)	3.90 (3.89)	16.66 (16.59)
3c	50	76	90	91	$C_{18}H_{13}FN_4S$	64.27 (67.29)	3.90 (3.88)	16.66 (16.59)
3d	40	78	90	90	$C_{18}H_{13}FN_4S$	64.27 (67.28)	3.90 (3.88)	16.66 (16.59)
3e	35	76	90	87	$C_{18}H_{13}ClN_4S$	61.27 (67.30)	3.71 (3.70)	15.88 (15.88)
3f	60	78	60	88	$C_{18}H_{13}ClN_4S$	61.27 (67.30)	3.71 (3.69)	15.88 (15.60)
3g	60	78	60	88	$C_{18}H_{13}ClN_4S$	61.27 (67.28)	3.71 (3.69)	15.88 (15.88)
3h	60	74	120	87	$C_{19}H_{16}N_4S$	68.65 (68.67)	4.85 (4.84)	16.85 (16.84)
3i	45	78	120	88	$C_{19}H_{16}N_4S$	68.65 (68.67)	4.85 (4.84)	16.85 (16.85)
3j	30	76	90	92	$C_{20}H_{18}N_4S$	69.34 (69.32)	5.24 (5.25)	16.17 (16.17)
3k	45	81	50	89	$C_{20}H_{18}N_4S$	69.34 (69.32)	5.24 (5.25)	16.17 (16.18)
3l	80	75	60	88	$C_{20}H_{18}N_4S$	69.34 (69.37)	5.24 (5.22)	16.17 (16.18)
3m	40	78	50	88	$C_{19}H_{16}N_4S$	68.65 (68.67)	4.85 (4.84)	16.85 (16.84)
3n	50	74	70	87	$C_{18}H_{21}N_5OS$	60.82 (60.84)	5.95 (5.93)	19.70 (19.70)
4a	45	80	100	93	$C_{18}H_{13}ClN_4S$	61.27 (61.30)	3.71 (3.70)	15.88 (15.90)
4b	30	80	90	86	$C_{18}H_{12}ClFN_4S$	58.30 (58.32)	3.26 (3.27)	15.11 (15.10)
4c	80	76	90	89	$C_{18}H_{12}ClFN_4S$	58.30 (58.31)	3.26 (3.27)	15.11 (15.10)
4d	50	81	90	82	$C_{18}H_{12}ClFN_4S$	58.30 (58.32)	3.26 (3.28)	15.11 (15.11)

Table 2 continued

Compounds	Reaction conditions				Mol. formula	Analysis %		
	Conventional		Microwave (210 W)			Calculated (found)		
	Time (min)	Yield (%)	Time (s)	Yield (%)		C	H	N
4e	35	78	60	84	$C_{18}H_{12}Cl_2N_4S$	55.82 (55.81)	3.12 (3.13)	14.47 (14.49)
4f	40	76	60	85	$C_{18}H_{12}Cl_2N_4S$	55.82 (55.84)	3.12 (3.12)	14.47 (14.47)
4g	45	75	60	88	$C_{18}H_{12}Cl_2N_4S$	55.82 (55.84)	3.12 (3.13)	14.47 (14.47)
4h	45	81	90	89	$C_{19}H_{15}ClN_4S$	62.20 (62.22)	4.12 (4.11)	15.27 (15.28)
4i	30	78	90	89	$C_{19}H_{15}ClN_4S$	62.20 (62.23)	4.12 (4.13)	15.27 (15.29)
4j	30	84	90	91	$C_{20}H_{17}ClN_4S$	63.07 (67.06)	4.50 (4.51)	14.71 (14.70)
4k	35	78	90	91	$C_{20}H_{17}ClN_4S$	63.07 (67.05)	4.50 (4.50)	14.71 (14.71)
4l	70	80	90	86	$C_{20}H_{17}ClN_4S$	63.07 (67.05)	4.50 (4.51)	14.71 (14.71)
4m	60	76	50	89	$C_{19}H_{15}ClN_4S$	62.20 (62.23)	4.12 (4.10)	15.27 (15.28)
4n	45	82	70	89	$C_{18}H_{20}ClN_5OS$	55.45 (55.46)	5.17 (5.17)	17.96 (17.97)

Isolated yields based on (2*Z*,4*Z*)-9-chloro-10-methyl/8-methyl/10-methyl/8-methoxy-*N*-aryl/alkyl-[1,3,4]thiadiazepino[7,6-*b*]quinolin-2-amines

(C=C), 1,384 (C–S).^{1}H NMR($CDCl_3$) δ: 2.52 (3H, s, C*H*$_3$), 7.57–7.94 (7H, m, Ar*H*), 8.36 (1H, s, Ar*H*), 8.58 (1H, s, Ar*H*), 9.20 (1H, s, *H*–C=N), 9.87 (1H, s, N*H*). MS *m/z*: 319 $[M+H]^+$.

(2Z,4Z)-N-(2-Fluorophenyl)-8-methyl-[1,3,4]thiadiazepino [7,6-b]quinolin-2-amine ***(1b)*** Yellow solid; m.p. 160 °C. IR (KBr) cm^{-1}: 3,480 (N–H), 1,637 (C=N), 1,384 (C–S).^{1}H NMR($CDCl_3$) δ: 2.54 (3H, s, C*H*$_3$), 7.87–7.94 (4H, m, Ar*H*), 8.47–8.55 (2H, m, Ar*H*), 8.94 (1H, s, Ar*H*), 9.18 (1H, s, Ar*H*), 9.41 (1H, s, *H*–C=N), 9.79 (1H, s, N*H*). MS *m/z*: 337 $[M+H]^+$.

(2Z,4Z)-N-(3-Fluorophenyl)-8-methyl-[1,3,4]thiadiazepino [7,6-b]quinolin-2-amine ***(1c)*** Yellow solid; m.p. 98 °C. IR (KBr) cm^{-1}: 3,490 (N–H), 1,638 (C=N), 1,384 (C–S). ^{1}H NMR($CDCl_3$) δ: 2.52 (3H, s, C*H*$_3$), 6.95 (1H, t, $J = 10.0$ Hz, Ar*H*), 7.24 (1H, s, Ar*H*), 7.58–7.69 (3H, m, Ar*H*), 7.90 (1H, d, $J = 11.2$ Hz, Ar*H*), 8.35 (1H, s, Ar*H*), 8.58 (1H, s, Ar*H*), 9.22 (1H, s, *H*–C=N), 9.73 (1H, s, N*H*). MS *m/z*: 337 $[M+H]^+$.

(2Z,4Z)-N-(4-Fluorophenyl)-8-methyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(1d)*** Yellow solid; m.p. 102 °C. IR (KBr) cm^{-1}: 3,490 (N–H), 1,638 (C=N), 1,384 (C–S). ^{1}H NMR($CDCl_3$) δ: 2.52 (3H, s, C*H*$_3$), 7.09 (1H, d, $J = 11.6$ Hz, Ar*H*), 7.58–7.63 (4H, m, Ar*H*), 7.90 (1H, d, $J = 11.6$ Hz, Ar*H*), 8.35 (1H, s, Ar*H*), 8.57 (1H, s, Ar*H*), 9.10 (1H, s, *H*–C=N), 9.81 (1H, s, N*H*). MS *m/z*: 337 $[M+H]^+$.

(2Z,4Z)-N-(2-Chlorophenyl)-8-methyl-[1,3,4]thiadiazepino [7,6-b]quinolin-2-amine ***(1e)*** Brownish yellow solid; m.p. 104 °C. IR (KBr) cm^{-1}: 3,400 (N–H), 1,617 (C=N), 1,547 (C=C), 1,384 (C–S). ^{1}H NMR($CDCl_3$) δ: 2.53 (3H, s, C*H*$_3$), 7.24 (1H, s, Ar*H*), 7.34 (1H, t, $J = 9.6$ Hz, Ar*H*), 7.45 (1H, d, $J = 10.4$ Hz, Ar*H*), 7.59 (1H, s, Ar*H*), 7.90 (1H, d, $J = 12.0$ Hz, Ar*H*), 8.36 (1H, s, Ar*H*), 8.63 (1H, s, Ar*H*), 8.70 (1H, d, $J = 10.0$ Hz, Ar*H*), 9.18 (1H, s, *H*–C=N), 9.67 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$, 355 $[M+H+2]^+$.

(2Z,4Z)-N-(3-Chlorophenyl)-8-methyl-[1,3,4]thiadiazepino [7,6-b]quinolin-2-amine ***(1f)*** Yellow solid; m.p. 102 °C. IR (KBr) cm^{-1}: 3,466 (N–H), 1,660 (C=N), 1,549, 1,585 (C=C), 1,384 (C–S). ^{1}H NMR($CDCl_3$) δ: 2.53 (3H, s, C*H*$_3$), 7.24 (1H, s, Ar*H*), 7.66 (3H, m, Ar*H*), 7.75 (1H, s, Ar*H*), 7.90 (1H, d, $J = 11.2$ Hz, Ar*H*), 8.35 (1H, s, Ar*H*), 8.58

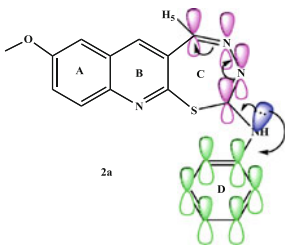


Fig. 2 Phenyl ring showing planarity with the orbitals of nitrogen and thiadiazepine ring

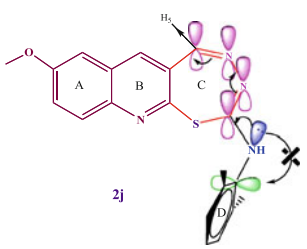


Fig. 3 Resonance effect operates through π framework to shield H_5 anti-bacterial activities

Table 3 Anti-bacterial activities of compounds **1a–n**, **2a–n**, **3a–n**, and **4a–n** tested by microdilution method (MIC mg/ml)

Entry	Compounds	Susceptible microorganism					
		Gram-positive bacteria			Gram-negative bacteria		
		B. subtilis	*S. aureus*	*S. pyogenes*	*E. coli*	*K. aerogenes*	*S. typhimurium*
1	**1a**	1.0	1.0	0.5	>1.0	0.5	0.5
2	**1b**	1.0	0.5	1.0	1.0	0.06	1.0
3	**1c**	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0
4	**1d**	0.25	0.25	0.5	0.5	0.125	0.25
5	**1e**	1.0	1.0	0.5	0.5	0.06	1.0
6	**1f**	1.0	1.0	>1.0	1.0	0.25	1.0
7	**1g**	1.0	1.0	>1.0	>1.0	1.0	>1.0
8	**1h**	0.5	0.5	0.5	1.0	0.5	1.0
9	**1i**	1.0	>1.0	1.0	1.0	0.06	0.06
10	**1j**	1.0	1.0	1.0	1.0	1.0	1.0
11	**1k**	0.5	0.5	0.5	0.5	0.5	0.5
12	**1l**	1.0	>1.0	>1.0	>1.0	>1.0	>1.0
13	**1m**	1.0	1.0	1.0	1.0	1.0	1.0
14	**1n**	>1.0	1.0	>1.0	0.5	1.0	1.0
15	**2a**	0.5	0.5	0.06	0.5	0.125	0.06
16	**2b**	1.0	0.5	0.5	1.0	>1.0	>1.0
17	**2c**	0.06	0.5	0.5	0.5	0.5	1.0
18	**2d**	0.5	0.5	0.5	0.5	0.06	0.25
19	**2e**	0.03	1.0	0.03	0.5	0.125	0.06
20	**2f**	0.06	0.5	0.03	0.03	0.25	0.5
21	**2g**	0.06	0.5	0.5	0.25	0.5	1.0
22	**2h**	1.0	1.0	1.0	0.5	1.0	0.125
23	**2i**	0.25	0.5	0.5	0.5	0.5	0.5
24	**2j**	1.0	1.0	0.5	0.5	0.5	0.5
25	**2k**	1.0	1.0	1.0	0.5	1.0	0.5
26	**2l**	0.5	0.5	0.5	0.5	0.5	0.5
27	**2m**	1.0	1.0	1.0	1.0	0.125	0.5
28	**2n**	0.5	0.5	0.5	0.5	1.0	0.5
29	**3a**	1.0	1.0	1.0	1.0	1.0	1.0
30	**3b**	0.5	1.0	1.0	0.5	0.5	0.25
31	**3c**	1.0	0.5	0.5	1.0	1.0	0.5
32	**3d**	0.5	0.25	0.25	0.25	0.5	0.5
33	**3e**	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0
34	**3f**	1.0	1.0	1.0	1.0	1.0	1.0
35	**3g**	1.0	1.0	1.0	1.0	1.0	1.0
36	**3h**	1.0	1.0	1.0	1.0	1.0	1.0
37	**3i**	1.0	1.0	1.0	1.0	1.0	1.0
38	**3j**	1.0	1.0	1.0	1.0	1.0	1.0
39	**3k**	1.0	1.0	1.0	1.0	1.0	1.0
40	**3l**	0.25	0.5	0.5	0.5	1.0	1.0
41	**3m**	>1.0	>1.0	>1.0	>1.0	1.0	>1.0
42	**3n**	1.0	1.0	1.0	1.0	1.0	1.0
43	**4a**	0.125	>1.0	0.06	0.06	0.06	>1.0
44	**4b**	0.06	0.5	0.06	0.5	0.5	0.5
45	**4c**	0.06	1.0	1.0	0.5	0.5	1.0
46	**4d**	0.125	1.0	0.06	0.5	1.0	1.0

Table 3 continued

Entry	Compounds	Susceptible microorganism					
		Gram-positive bacteria			Gram-negative bacteria		
		B. subtilis	*S. aureus*	*S. pyogenes*	*E. coli*	*K. aerogenes*	*S. typhimurium*
47	**4e**	0.5	0.5	0.5	0.5	0.5	0.5
48	**4f**	0.125	0.5	0.125	0.06	1.0	1.0
49	**4g**	0.06	1.0	0.5	0.5	0.5	1.0
50	**4h**	0.06	0.5	0.25	0.25	0.25	0.5
51	**4i**	0.125	0.5	0.25	0.25	0.5	0.5
52	**4j**	0.06	0.5	0.06	0.125	0.5	1.0
53	**4k**	0.03	0.5	0.06	0.06	0.5	0.5
54	**4l**	0.125	1.0	0.5	1.0	1.0	1.0
55	**4m**	0.06	1.0	1.0	1.0	0.5	0.06
56	**4n**	0.25	0.25	0.25	0.5	0.25	0.125
	Chloramphenicol	1.0	1.0	1.0	1.0	1.0	1.0

(1H, s, Ar*H*), 9.18 (1H, s, *H*–C=N), 9.67 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$, 355 $[M+H+2]^+$.

*(2Z,4Z)-N-(4-Chlorophenyl)-8-methyl-[1,3,4]thiadiazepino [7,6-b]quinolin-2-amine (**1g**)* Yellow solid; m.p. 98 °C. IR (KBr) cm^{-1}: 3,491 (N–H), 1,637 (C=N), 1,549 (C=C), 1,384 (C–S). ^1H NMR($CDCl_3$) δ: 2.51 (3H, s, CH_3), 7.24–7.36 (4H, m, Ar*H*), 7.58 (1H, d, $J = 11.2$ Hz, Ar*H*), 7.88 (1H, d, $J = 11.6$ Hz, Ar*H*), 8.38 (1H, s, Ar*H*), 8.56 (1H, s, Ar*H*), 9.15 (1H, s, *H*–C=N), 10.06 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$, 355 $[M+H+2]^+$.

*(2Z,4Z)-8-Methyl-N-o-tolyl-[1,3,4]thiadiazepino[7,6-b] quinolin-2-amine (**1h**)* Yellow solid; m.p. 196 °C. IR (KBr) cm^{-1}: 3,492 (N–H), 1,616 (C=N), 1,384 (C–S).^1H NMR($CDCl_3$) δ: 2.44 (3H, s, CH_3), 3.38 (3H, s, CH_3), 7.24 (2H, s, Ar*H*), 7.51 (1H, s, Ar*H*), 7.53 (1H, s, Ar*H*), 7.78 (1H, s, Ar*H*), 7.87 (1H, s, Ar*H*), 8.36 (1H, s, Ar*H*), 8.57 (1H, s, Ar*H*), 8.96 (1H, s, *H*–C=N), 9.09 (1H, s, N*H*). MS *m/z*: 333 $[M+H]^+$.

*(2Z,4Z)-8-Methyl-N-p-tolyl-[1,3,4]thiadiazepino[7,6-b] quinolin-2-amine (**1i**)* Brown solid; m.p. 90 °C. IR (KBr) cm^{-1}: 3,433 (N–H), 1,636 (C=N), 1,384 (C–S).^1H NMR($CDCl_3$) δ: 2.36 (3H, s, CH_3), 2.52 (3H, s, CH_3), 7.24 (2H, s, Ar*H*), 7.51 (2H, d, $J = 8.4$ Hz, Ar*H*), 7.91 (2H, d, $J = 8.8$ Hz, Ar*H*), 8.58 (1H, s, Ar*H*), 8.94 (1H, s, Ar*H*), 9.11 (1H, s, Ar*H*), 9.18 (1H, s, *H*–C=N), 9.78 (1H, s, N*H*). MS *m/z*: 333 $[M+H]^+$.

*(2Z,4Z)-8-Methyl-N-(2,6-dimethylphenyl)-[1,3,4]thiadiaze-pino[7,6-b]quinolin-2-amine (**1j**)* Yellow solid; m.p. 170 °C. IR (KBr) cm^{-1}: 3,440 (N–H), 1,622 (C=N), 1,413 (C=C), 1,384 (C–S). ^1H NMR($CDCl_3$) δ: 2.32 (6H, s, CH_3 × 2), 2.35 (3H, s, CH_3), 7.12 (1H, d, $J = 8.0$ Hz, Ar*H*), 7.14 (2H, d, $J = 7.6$ Hz, Ar*H*), 7.45 (1H, dd, $J = 2.8$, 7.8 Hz, Ar*H*), 7.93 (1H, d, $J = 9.1$ Hz, Ar*H*), 8.35 (1H, s, Ar*H*), 8.55 (1H, s, Ar*H*), 8.65 (1H, s, *H*–C=N), 9.70 (1H, s, N*H*). MS *m/z*: 347 $[M+H]^+$.

*(2Z,4Z)-8-Methyl-N-(2,4-dimethylphenyl)-[1,3,4]thiadiaze-pino[7,6-b]quinolin-2-amine (**1k**)* Yellow solid; m.p. 184 °C.IR (KBr) cm^{-1}: 3,467 (N–H), 1,636 (C=N), 1,384 (C–S).^1H NMR ($CDCl_3$) δ: 2.45 (3H, s, CH_3), 3.84 (6H, s, CH_3 × 2), 7.01 (1H, d, $J = 8.4$ Hz, Ar*H*), 7.24 (1H, s, Ar*H*), 7.53 (1H, d, $J = 8.4$ Hz, Ar*H*), 7.57 (1H, s, Ar*H*), 7.81 (1H, s, Ar*H*), 8.36 (1H, s, Ar*H*), 8.58 (1H, s, Ar*H*), 8.89 (1H, s, *H*–C=N), 9.11 (1H, s, N*H*). MS *m/z*: 347 $[M+H]^+$.

*(2Z,4Z)-N-(4-Ethylphenyl)-8-methyl-[1,3,4]thiadiazepino [7,6-b]quinolin-2-amine (**1l**)* Yellow solid; m.p. 100 °C.IR (KBr) cm^{-1}: 3,400 (N–H), 1,621 (C=N), 1,548, 1,529 (C=C), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 1.24 (3H, t, $J = 7.5$ Hz, CH_3), 2.66 (2H, q, $J = 7.8$ Hz, CH_2), 2.52 (3H, s, CH_3), 7.53–7.63 (4H, m, Ar*H*), 7.23 (1H, s, Ar*H*), 7.89 (1H, d, $J = 11.6$ Hz, Ar*H*), 8.34 (1H, s, Ar*H*), 8.57 (1H, s, Ar*H*), 9.18 (1H, s, *H*–C=N), 9.83(1H, s, N*H*). MS *m/z*: 347 $[M+H]^+$.

*(2Z,4Z)-N-benzyl-8-methyl-[1,3,4]thiadiazepino[7,6-b] quinolin-2-amine (**1m**)* Yellow solid; m.p. 192 °C.IR (KBr) cm^{-1}: 3,410 (N–H), 1,637 (C=N), 1,546 (C=C), 1,384 (C–S).^1H NMR ($CDCl_3$) δ: 2.44 (3H, s, CH_3), 4.93 (2H, d, $J = 4$ Hz, CH_2), 7.24–7.35 (3H, m, Ar*H*), 7.54 (1H, s, Ar*H*), 7.51 (1H, d, $J = 8.8$ Hz, Ar*H*), 7.79 (1H, d, $J = 8.8$ Hz, Ar*H*), 7.81 (1H, s, Ar*H*), 8.10 (1H, s, Ar*H*), 8.18 (1H, s, Ar*H*), 8.29 (1H, s, *H*–C=N), 8.48 (1H, s, N*H*). MS *m/z*: 333 $[M+H]^+$.

Table 4 Anti-fungal activities of compounds **1a–n**, **2a–n**, **3a–n**, and **4a–n** tested by microdilution method (MIC mg/ml)

Entry	Compounds	Susceptible microorganism				
		T. reesei	*A. flavus*	*A. alternata*	*A. niger*	*D. australiensis*
1	**1a**	0.5	0.5	1.0	1.0	>1.0
2	**1b**	1.0	>1.0	1.0	>1.0	>1.0
3	**1c**	1.0	1.0	0.5	1.0	>1.0
4	**1d**	1.0	>1.0	1.0	1.0	>1.0
5	**1e**	1.0	0.5	1.0	>1.0	1.0
6	**1f**	0.5	1.0	0.5	1.0	1.0
7	**1g**	0.5	1.0	0.03	0.5	0.5
8	**1h**	0.125	0.125	1.0	0.25	1.0
9	**1i**	0.5	1.0	0.5	1.0	1.0
10	**1j**	0.25	1.0	0.5	1.0	1.0
11	**1k**	0.125	0.5	0.5	1.0	0.5
12	**1l**	0.5	1.0	0.5	0.5	1.0
13	**1m**	0.5	>1.0	1.0	1.0	1.0
14	**1n**	0.25	0.5	0.5	0.5	0.5
15	**2a**	1.0	0.5	0.5	0.5	0.5
16	**2b**	0.25	0.5	0.125	0.5	0.5
17	**2c**	1.0	0.5	0.5	1.0	0.5
18	**2d**	0.5	>1.0	0.06	1.0	1.0
19	**2e**	0.5	0.5	0.5	0.5	0.5
20	**2f**	0.5	0.5	0.06	0.5	0.5
21	**2g**	0.25	0.5	0.03	0.5	0.5
22	**2h**	0.5	0.5	1.0	1.0	1.0
23	**2i**	1.0	1.0	0.5	>1.0	0.5
24	**2j**	0.5	0.5	1.0	1.0	0.5
25	**2k**	0.5	1.0	0.25	1.0	0.5
26	**2l**	0.5	0.5	0.5	0.5	1.0
27	**2m**	0.5	1.0	1.0	1.0	1.0
28	**2n**	1.0	0.5	1.0	1.0	1.0
29	**3a**	0.5	1.0	1.0	1.0	>1.0
30	**3b**	1.0	1.0	1.0	>1.0	1.0
31	**3c**	0.5	1.0	0.5	1.0	1.0
32	**3d**	0.5	1.0	0.5	1.0	1.0
33	**3e**	1.0	1.0	1.0	>1.0	0.5
34	**3f**	1.0	1.0	0.5	0.5	1.0
35	**3g**	1.0	0.25	0.5	1.0	0.5
36	**3h**	0.125	0.125	1.0	0.5	0.5
37	**3i**	0.5	0.5	1.0	1.0	1.0
38	**3j**	0.25	0.5	0.5	1.0	1.0
39	**3k**	0.25	0.5	0.5	1.0	0.5
40	**3l**	0.5	1.0	0.5	0.5	0.5
41	**3m**	1.0	1.0	1.0	0.5	1.0
42	**3n**	0.25	0.25	0.5	0.5	0.5
43	**4a**	0.25	0.5	0.25	1.0	1.0
44	**4b**	0.25	0.5	0.5	0.5	1.0
45	**4c**	0.25	1.0	1.0	1.0	1.0
46	**4d**	0.25	0.5	0.25	0.5	0.5
47	**4e**	0.06	0.5	0.06	0.5	0.25
48	**4f**	0.25	0.5	0.5	0.5	1.0
49	**4g**	0.125	1.0	0.25	0.5	0.5
50	**4h**	0.06	1.0	0.25	0.5	0.5
51	**4i**	0.25	1.0	0.5	1.0	1.0
52	**4j**	0.25	0.5	0.125	0.5	0.5
53	**4k**	0.25	0.5	0.25	0.5	0.5
54	**4l**	1.0	>1.0	1.0	1.0	>1.0
55	**4m**	0.5	0.5	0.5	0.5	0.5
56	**4n**	1.0	1.0	1.0	1.0	1.0
	Mancozeb	0.25	0.25	0.25	0.25	0.25

*(2Z,4Z)-8-Methyl-N-(2-morpholinoethyl)-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**1n**)* Yellow solid; m.p. 210 °C.IR (KBr) cm^{-1}: 3,468 (N–H), 1,660 (C=N), 1,549, 1,585 (C=C), 1,384 (C–S).^{1}H NMR ($CDCl_3$) δ: 2.48 (3H, s, CH_3), 2.52 (4H, s, CH_2 × 2), 2.64–2.72 (2H, m, CH_2) 3.73–3.78 (6H, m, CH_2 × 3), 7.24 (1H, s, Ar*H*), 7.55 (2H, d, J = 7.2 Hz, Ar*H*), 7.83 (1H, d, J = 8.8 Hz, Ar*H*), 8.26 (1H, s, *H*–C=N), 8.58 (1H, s, N*H*). MS *m/z*: 356 $[M+H]^+$.

*(2Z,4Z)-8-Methoxy-N-phenyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**2a**)* Yellow solid; m.p. 174 °C. IR (KBr) cm^{-1}: 3,464 (N–H), 1,636 (C=N), 1,384 (C–S).^{1}H NMR($CDCl_3$) δ: 3.92 (3H, s, OCH_3), 7.12 (1H, d, J = 2.8 Hz, Ar*H*), 7.39–7.45 (3H, m, Ar*H*), 7.66 (2H, d, J = 8.0 Hz, Ar*H*), 7.89 (1H, d, J = 9.2 Hz, Ar*H*), 8.33 (1H, s, Ar*H*), 8.56 (1H, s, Ar*H*), 9.19 (1H, s, *H*–C=N), 9.73 (1H, s, N*H*). MS *m/z*: 335 $[M+H]^+$.

*(2Z,4Z)-N-(2-Fluorophenyl)-8-methoxy-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**2b**)* Yellow solid; m.p. 190 °C. IR (KBr) cm^{-1}: 3,495 (N–H), 1,640 (C=N), 1,384 (C–S).^{1}H NMR($CDCl_3$) δ: 3.93 (3H, s, OCH_3), 7.1 (1H, d, J = 2.4 Hz, Ar*H*), 7.19–7.21 (2H, m, Ar*H*), 7.41 (1H, dd, J = 2.8 Hz, Ar*H*), 7.90 (1H, d, J = 9.2 Hz, Ar*H*), 8.32 (1H, s, Ar*H*), 8.46–8.50 (1H, m, Ar*H*), 8.59 (1H, s, Ar*H*), 9.37 (1H, s, *H*–C=N), 9.53 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$.

*(2Z,4Z)-N-(3-Fluorophenyl)-8-methoxy-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**2c**)* Yellow solid; m.p. 156 °C. IR (KBr) cm^{-1}: 3,476 (N–H), 1,617 (C=N), 1,548, 1,531 (C=C) 1,384 (C–S). ^{1}H NMR($CDCl_3$) δ: 3.92 (3H, s, OCH_3), 6.95 (1H, d, J = 9.6 Hz, Ar*H*), 7.24 (1H, s, Ar*H*), 7.58–7.69 (3H, m, Ar*H*), 7.90 (1H, d, J = 11.2 Hz, Ar*H*),

8.32 (1H, s, Ar*H*), 8.55 (1H, s, Ar*H*), 9.20 (1H, s, *H*–C=N), 9.74 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$.

(2Z,4Z)-N-(4-Fuorophenyl)-8-methoxy-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2d)*** Yellow solid; m.p. 160 °C. IR (KBr) cm^{-1}: 3,490 (N–H), 1,617 (C=N), 1,549 (C=C), 1,384 (C–S). ^1H NMR($CDCl_3$) δ: 3.92 (3H, s, OCH_3), 7.08–7.13 (4H, m, Ar*H*), 7.57–7.61 (2H, m, Ar*H*), 8.30 (1H, s, Ar*H*), 8.57 (1H, s, Ar*H*), 9.18 (1H, s, *H*–C=N), 9.48 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$.

(2Z,4Z)-N-(2-Chlorophenyl)-8-methoxy-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2e)*** Brownish solid; m.p. 86 °C. IR (KBr) cm^{-1}: 3,405 (N–H), 1,660 (C=N), 1,549, 1,585 (C=C), 1,384 (C–S). ^1H NMR($CDCl_3$) δ: 3.93 (3H, s, OCH_3), 7.0 (1H, d, $J = 2.8$ Hz, Ar*H*), 7.24 (1H, s, Ar*H*), 7.42 (1H, d, $J = 2.4$ Hz, Ar*H*), 8.0 (1H, s, Ar*H*), 8.34 (1H, s, Ar*H*), 8.61 (1H, s, Ar*H*), 8.94 (1H, s, Ar*H*), 9.16 (1H, s, Ar*H*), 9.59 (1H, s, *H*–C=N), 9.77 (1H, s, N*H*). MS *m/z*: 369 $[M+H]^+$, 371 $[M+H+2]^+$.

(2Z,4Z)-N-(3-Chlorophenyl)-8-methoxy-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2f)*** Yellow solid; m.p. 82 °C. IR (KBr) cm^{-1}: 3,410 (N–H), 1,641 (C=N), 1,384 (C–S). ^1H NMR($CDCl_3$) δ: 3.93 (3H, s, OCH_3), 7.14 (1H, d, $J = 2.8$ Hz, Ar*H*), 7.23 (1H, d, $J = 8.8$ Hz, Ar*H*), 7.41 (1H, dd, $J = 2.8$ Hz, Ar*H*), 7.64 (1H, d, $J = 8.0$ Hz, Ar*H*), 7.73 (1H, s, Ar*H*), 7.90 (1H, d, $J = 9.6$ Hz, Ar*H*), 8.34 (1H, s, Ar*H*), 8.56 (1H, s, Ar*H*), 9.16 (1H, s, *H*–C=N), 9.66 (1H, s, N*H*). MS *m/z*: 369 $[M+H]^+$, 371 $[M+H+2]^+$.

(2Z,4Z)-N-(4-Chlorophenyl)-8-methoxy-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2g)*** Yellow solid; m.p. 102 °C. IR (KBr) cm^{-1}: 3,420 (N–H), 1,619 (C=N), 1,547, 1,529 (C=C), 1,384 (C–S).^1H NMR($CDCl_3$) δ: 3.92 (3H, s, OCH_3), 7.36 (2H, d, $J = 8.8$ Hz Ar*H*), 7.62 (2H, d, $J = 8.8$ Hz, Ar*H*), 7.89 (2H, d, $J = 9.2$ Hz, Ar*H*), 8.33 (1H, s, Ar*H*), 8.56 (1H, s, Ar*H*), 9.16 (1H, s, *H*–C=N), 9.67 (1H, s, N*H*). MS *m/z*: 369 $[M+H]^+$, 371 $[M+H+2]^+$.

(2Z,4Z)-8-Methoxy-N-o-tolyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2h)*** Yellow solid; m.p. 198 °C. IR (KBr) cm^{-1}: 3,404 (N–H), 1,619 (C=N), 1,547, 1,528 (C=C), 1,384 (C–S). ^1H NMR($CDCl_3$) δ: 2.37 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 7.09 (1H, d, $J = 2.8$ Hz, Ar*H*), 7.28 (1H, s, Ar*H*), 7.40 (1H, dd, $J = 2.8$ Hz, Ar*H*), 7.60 (1H, d, $J = 7.6$ Hz, Ar*H*), 7.90 (1H, d, $J = 9.6$ Hz, Ar*H*), 8.33 (1H, s, Ar*H*), 8.55 (1H, s, Ar*H*), 8.90 (1H, s, Ar*H*), 8.98 (1H, s, *H*–C=N), 9.68 (1H, s, N*H*). MS *m/z*: 349 $[M+H]^+$.

(2Z,4Z)-8-methoxy-N-p-tolyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2i)*** Yellow solid; m.p. 90 °C. IR (KBr) cm^{-1}: 3,437 (N–H), 1,624 (C=N), 1,529, 1,495 (C=C), 1,384 (C–S). ^1H NMR($CDCl_3$) δ: 2.36 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 7.24 (1H, s, Ar*H*), 7.50 (2H, d, $J = 8.0$ Hz, Ar*H*), 7.89 (2H, d, $J = 9.2$ Hz, Ar*H*), 8.31 (1H, s, Ar*H*), 8.57 (1H, s, Ar*H*), 8.94 (1H, s, Ar*H*), 9.10 (1H, s, *H*–C=N),9.63 (1H, s, N*H*). MS *m/z*: 349 $[M+H]^+$.

(2Z,4Z)-8-Methoxy-N-(2,6-dimethylphenyl)-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2j)*** Yellow solid; m.p. 218 °C. IR (KBr) cm^{-1}: 3,406 (N–H), 1,635 (C=N), 1,495 (C=C), 1,384 (C–S). ^1H NMR($CDCl_3$) δ: 2.34 (6H, s, $CH_3 \times 2$), 3.90 (3H, s, OCH_3), 7.10 (1H, d, $J = 2.4$ Hz, Ar*H*), 7.14 (2H, d, $J = 7.6$ Hz, Ar*H*), 7.39–7.42 (1H, dd, $J = 2.4$, 2.8 Hz, Ar*H*), 7.90 (1H, d, $J = 9.2$ Hz, Ar*H*), 8.34 (1H, s, Ar*H*), 8.56 (1H, s, Ar*H*), 8.69 (1H, s, *H*–C=N), 9.73 (1H, s, N*H*). MS *m/z*: 363 $[M+H]^+$.

(2Z,4Z)-8-Methoxy-N-(2,4-dimethylphenyl)-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2k)*** Yellow solid; m.p. 208 °C. IR (KBr) cm^{-1}: 3,467 (N–H), 1,618 (C=N), 1,528, 1,495 (C=C), 1,384 (C–S).^1H NMR($CDCl_3$) δ: 2.32 (3H, s, CH_3), 2.33 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 7.08 (2H, m, Ar*H*), 7.24 (1H, s, Ar*H*), 7.40 (1H, d, $J = 8.4$ Hz, $J = 2.8$ Hz, Ar*H*), 7.89 (1H, d, $J = 9.2$ Hz, Ar*H*), 8.33 (1H, s, Ar*H*), 8.55 (1H, s, Ar*H*), 8.87 (1H, s, *H*–C=N), 9.72 (1H, s, N*H*). MS *m/z*: 363 $[M+H]^+$.

(2Z,4Z)-N-(4-Ethylphenyl)-8-methoxy-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2l)*** Yellow solid; m.p. 90 °C. IR (KBr) cm^{-1}: 3,466 (N–H), 1,622 (C=N), 1,547, 1,528 (C=C), 1,384 (C–S).^1H NMR($CDCl_3$) δ: 1.24 (3H, t, $J = 7.6$ Hz, CH_3), 2.66 (2H, q, $J = 7.6$ Hz, CH_2), 3.92 (3H, s, OCH_3), 7.11 (1H, d, $J = 2.4$ Hz, Ar*H*), 7.24 (1H, s, Ar*H*), 7.41 (1H, dd, $J = 2.8$ Hz, Ar*H*), 7.54 (2H, d, $J = 8.4$ Hz, Ar*H*), 7.90 (1H, d, $J = 9.2$ Hz, Ar*H*), 8.28 (1H, s, Ar*H*), 8.57 (1H, s, Ar*H*), 9.11 (1H, s, *H*–C=N), 9.40 (1H, s, N*H*). MS *m/z*: 363 $[M+H]^+$.

(2Z,4Z)-N-benzyl-8-methoxy-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2m)*** Yellow solid; m.p. 206 °C. IR (KBr) cm^{-1}: 3,460 (N–H), 1,623 (C=N), 1,548, 1,529 (C=C), 1,384 (C–S).^1H NMR($CDCl_3$) δ: 3.89 (3H, s, OCH_3), 5.01 (2H, d, $J = 6.0$ Hz, CH_2), 7.00 (1H, d, $J = 2.8$ Hz, Ar*H*), 7.30–7.45 (5H, m, Ar*H*), 7.75 (1H, s, Ar*H*), 7.87 (1H, d, $J = 9.2$ Hz, Ar*H*,), 8.25 (1H, s, Ar*H*), 8.47 (1H, s, *H*–C=N), 9.46 (1H, s, N*H*). MS *m/z*: 349 $[M+H]^+$.

(2Z,4Z)-8-Methoxy-N-(2-morpholinoethyl)-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine ***(2n)*** Yellow solid; m.p. 200 °C. IR (KBr) cm^{-1}: 3,480 (N–H), 1,620 (C=N), 1,539, 1,496 (C=C), 1,384 (C–S).^1H NMR($CDCl_3$) δ: 2.57 (4H, t, $J = 4.4$ Hz, $J = 4.0$ Hz, $CH_2 \times 2$), 2.69 (2H, t, $J = 6.4$ Hz,

$J = 6.0$ Hz, CH_2), 3.78–3.83 (6H, m, $CH_2 \times 3$), 3.91 (3H, s, OCH_3), 7.00 (1H, d, $J = 2.8$ Hz, Ar*H*), 7.40 (1H, dd, $J = 2.8$ Hz, Ar*H*), 7.89 (1H, d, $J = 9.2$ Hz, Ar*H*), 8.21 (1H, s, Ar*H*), 8.59 (1H, s, *H*–C=N), 9.38 (1H, s, N*H*). MS *m/z*: 372 $[M+H]^+$.

*(2Z,4Z)-10-Methyl-N-phenyl-[1,3,4]thiadiazepino[7,6-b] quinolin-2-amine (**3a**)* Yellow solid; m.p. 210 °C. IR (KBr) cm^{-1}: 3,432 (N–H), 1,660 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 7.61 (2H, d, $J = 8.4$ Hz, Ar*H*), 7.67 (2H, d, $J = 8.0$ Hz, Ar*H*), 7.72 (1H, d, $J = 8.0$ Hz, Ar*H*), 7.78 (1H, d, $J = 8.0$ Hz, Ar*H*), 8.32 (1H, s, Ar*H*), 8.64 (1H, s, Ar*H*), 8.99 (1H, s, Ar*H*), 9.19 (1H, s, *H*–C=N), 9.42 (1H, s, N*H*). MS *m/z*: 319 $[M+H]^+$.

*(2Z,4Z)-N-(2-Fluorophenyl)-10-methyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**3b**)* Yellow solid; m.p. 200 °C. IR (KBr) cm^{-1}: 3,439 (N–H), 1,627 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 7.17–7.21 (2H, m, Ar*H*), 7.46–7.51 (2H, m, Ar*H*), 7.61 (1H, d, $J = 7.2$ Hz, Ar*H*), 7.73 (1H, d, $J = 8.4$ Hz, Ar*H*), 8.35 (1H, s, Ar*H*), 8.66 (1H, s, Ar*H*), 9.40 (1H, s, *H*–C=N), 9.56 (1H, s, N*H*). MS *m/z*: 337 $[M+H]^+$.

*(2Z,4Z)-N-(3-Fluorophenyl)-10-methyl-[1,3,4]thiadiazepino[7,6-b] quinolin-2-amine (**3c**)* Yellow solid; m.p. 138 °C. IR (KBr) cm^{-1}: 3,490 (N–H), 1,616 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 6.93–6.97 (1H, m, Ar*H*), 7.41 (1H, d, $J = 8.4$ Hz, Ar*H*), 7.46–7.51 (2H, m, Ar*H*), 7.62–7.64 (1H, d, Ar*H*), 7.73 (1H, d, $J = 8.0$ Hz, Ar*H*), 8.35 (1H, s, Ar*H*), 8.63 (1H, s, Ar*H*), 9.21 (1H, s, *H*–C=N), 9.59 (1H, s, N*H*). MS *m/z*: 337 $[M+H]^+$.

*(2Z,4Z)-N-(4-Fluorophenyl)-10-methyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**3d**)* Yield: 90 %. Dark yellow solid; m.p. 88 °C. IR (KBr) cm^{-1}: 3,441 (N–H), 1,637 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 7.10 (1H, s, Ar*H*), 7.48 (1H, d, $J = 8.0$ Hz, Ar*H*), 7.57–7.64 (3H, m, Ar*H*), 7.71 (1H, d, $J = 8.0$ Hz, Ar*H*), 8.35 (1H, s, Ar*H*), 8.64 (1H, s, Ar*H*), 9.09 (1H, s, *H*–C=N), 9.55 (1H, s, N*H*). MS *m/z*: 337 $[M+H]^+$.

*(2Z,4Z)-N-(2-Chlorophenyl)-10-methyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**3e**)* Dark yellow solid; m.p. 100 °C. IR (KBr) cm^{-1}: 3,478 (N–H), 1,635 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 7.32–7.36 (1H, m, Ar*H*), 7.61 (2H, d, $J = 8.8$ Hz, Ar*H*), 7.69 (1H, d, $J = 8.0$ Hz, Ar*H*), 7.78 (1H, d, $J = 8.0$ Hz, Ar*H*), 8.36 (1H, s, Ar*H*), 8.69 (2H, s, Ar*H*), 9.52 (1H, s, *H*–C=N), 9.83 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$, 355 $[M+H+2]^+$.

*(2Z,4Z)-N-(3-Chlorophenyl)-10-methyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**3f**)* Yellow solid; m.p. 120 °C. IR (KBr) cm^{-1}: 3,456 (N–H), 1,618 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 7.33 (1H, t, $J = 8.0$ Hz, Ar*H*), 7.46–7.51 (2H, m, Ar*H*), 7.62 (2H, d, $J = 7.2$ Hz, Ar*H*), 7.75 (1H, s, Ar*H*), 8.35 (1H, s, Ar*H*), 8.63 (1H, s, Ar*H*), 9.17 (1H, s, *H*–C=N), 9.53 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$, 355 $[M+H+2]^+$.

*(2Z,4Z)-N-(4-Chlorophenyl)-10-methyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**3g**)* Yellow solid; m.p. 108 °C. IR (KBr) cm^{-1}: 3,484 (N–H), 1,616 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 7.37 (2H, d, $J = 8.4$ Hz, Ar*H*), 7.46–7.51 (2H, m, Ar*H*), 7.62 (1H, s, Ar*H*), 7.72 (1H, d, $J = 8.0$ Hz, Ar*H*), 8.36 (1H, s, Ar*H*), 8.63 (1H, s, Ar*H*), 9.14 (1H, s, *H*–C=N), 9.63 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$, 355 $[M+H+2]^+$.

*(2Z,4Z)-10-Methyl-N-o-tolyl-[1,3,4]thiadiazepino[7,6-b] quinolin-2-amine (**3h**)* Yellow solid; m.p. 214 °C. IR (KBr) cm^{-1}: 3,424 (N–H), 1,617 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 2.37 (3H, s, ArCH_3), 7.45–7.48 (2H, m, Ar*H*), 7.60–7.70 (4H, m, Ar*H*), 8.34 (1H, s, Ar*H*), 8.61 (1H, s, Ar*H*), 8.99 (1H, s, *H*–C=N), 9.55 (1H, s, N*H*). MS *m/z*: 333 $[M+H]^+$.

*(2Z,4Z)-10-Methyl-N-p-tolyl-[1,3,4]thiadiazepino[7,6-b] quinolin-2-amine (**3i**)* Dark yellow solid; m.p. 200 °C. IR (KBr) cm^{-1}: 3,420 (N–H), 1,637 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 2.36 (3H, s, ArCH_3), 7.45–7.52 (4H, m, Ar*H*), 7.61 (1H, d, $J = 7.2$ Hz, Ar*H*), 7.72 (1H, d, $J = 8.0$ Hz, Ar*H*), 8.31 (1H, s, Ar*H*), 8.64 (1H, s, Ar*H*), 9.10 (1H, s, *H*–C=N), 9.39 (1H, s, N*H*). MS *m/z*: 333 $[M+H]^+$.

*(2Z,4Z)-10-Methyl-N-(2,6-dimethylphenyl)-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**3j**)* Light yellow solid; m.p. 216 °C. IR (KBr) cm^{-1}: 3,480 (N–H), 1,637 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.76 (3H, s, ArCH_3), 2.33 (6H, s, ArCH_3), 7.14 (2H, d, $J = 7.2$ Hz, Ar*H*), 7.47 (1H, d, $J = 8.0$ Hz, Ar*H*), 7.61 (1H, d, $J = 6.8$ Hz, Ar*H*), 7.70 (1H, d, $J = 8.0$ Hz, Ar*H*), 8.32 (1H, s, Ar*H*), 8.62 (1H, s, Ar*H*), 8.68 (1H, s, *H*–C=N), 9.43 (1H, s, N*H*). MS *m/z*: 347 $[M+H]^+$.

*(2Z,4Z)-10-Methyl-N-(2,4-dimethylphenyl)-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**3k**)* Light yellow solid; m.p. 210 °C. IR (KBr) cm^{-1}: 3,414 (N–H), 1,624 (C=N), C–S (1,383). ^1H NMR: ($CDCl_3$) δ: 2.76 (3H, s, ArCH_3), 2.31 (6H, s, ArCH_3), 7.09 (1H, s, Ar*H*), 7.43–7.51 (2H, m, Ar*H*), 7.69 (1H, d, $J = 8.4$ Hz, Ar*H*), 7.78 (1H, d, $J = 8.0$ Hz, Ar*H*), 8.32 (1H, s, Ar*H*), 8.62 (1H, s, Ar*H*),

8.89 (1H, s, *H*–C=N), 9.49 (1H, s, N*H*). MS *m/z*: 347 $[M+H]^+$.

(2Z,4Z)-N-(4-Ethylphenyl)-10-methyl-[1,3,4]thiadiazepino [7,6-b]quinolin-2-amine ***(3l)*** Yellow solid; m.p. 194 °C.IR (KBr) cm^{-1}: 3,440 (N–H), 1,637 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 1.24 (3H, t, $J = 8.0$ Hz, CH_3), 2.66 (2H, q, $J = 7.6$ Hz, CH_2), 2.75 (3H, s, ArCH_3), 7.25 (1H, s, Ar*H*),7.48 (1H, d, $J = 8.0$ Hz, Ar*H*), 7.54 (2H, d, $J = 8.0$ Hz, Ar*H*), 7.61 (1H, d, $J = 7.2$ Hz, Ar*H*), 7.72 (1H, d, $J = 8.0$ Hz, Ar*H*), 8.30 (1H, s, Ar*H*), 8.63 (1H, s, Ar*H*), 9.12 (1H, s, *H*–C=N), 9.33 (1H, s, N*H*). MS *m/z*:347 $[M+H]^+$.

(2Z,4Z)-N-Benzyl-10-methyl-[1,3,4]thiadiazepino[7,6-b] quinolin-2-amine ***(3m)*** Yellow solid; m.p. 188 °C.IR (KBr) cm^{-1}: 3,410 (N–H), 1,637 (C=N), 1,384 (C–S). ^1H NMR($CDCl_3$) δ: 2.73 (3H, s, ArCH_3), 5.00 (2H, d, $J = 5.6$, CH_2), 7.30 (1H, d, $J = 7.2$ Hz, Ar*H*), 7.33–745 (4H, m, Ar*H*), 7.58 (1H, d, $J = 6.8$ Hz, Ar*H*), 7.66 (1H, d, $J = 8.4$ Hz, Ar*H*), 7.75 (1H, s, Ar*H*), 8.26 (1H, s, Ar*H*), 8.53 (1H, s, *H*–C=N), 9.42 (1H, s, N*H*). MS *m/z*: 333 $[M+H]^+$.

(2Z,4Z)-10-Methyl-N-(2-morpholinoethyl)-[1,3,4]thiadiaze-pino[7,6-b]quinolin-2-amine ***(3n)*** Light yellow solid; m.p. 202 °C. IR (KBr) cm^{-1}: 3,420 (N–H), 1,637 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s, ArCH_3), 2.57 (4H, s,CH_2), 2.69 (2H, t, $J = 5.6$ CH_2), 3.80 (6H, m, CH_2), 7.60–7.65 (2H, m, Ar*H*), 8.21 (2H, s, Ar*H*), 8.62 (1H, s, *H*–C=N), 9.13 (1H, s, N*H*). MS *m/z*: 356 $[M+H]^+$.

(2Z,4Z)-9-Chloro-10-methyl-N-phenyl-[1,3,4]thiadiazepi-no[7,6-b]quinolin-2-amine ***(4a)*** Light yellow solid; m.p. 220 °C. IR (KBr) cm^{-1}: 3,442 (N–H), 1,630 (C=N), 1,384 (C–S). ^1H NMR: ($CDCl_3$) δ: 2.81 (3H, s, ArCH_3), 7.25 (1H, d, $J = 7.6$ Hz, Ar*H*), 7.40 (2H, d, $J = 8.0$ Hz, Ar*H*), 7.66 (3H, d, $J = 8.0$, Ar*H*), 8.32 (1H, s, Ar*H*), 8.61 (1H, s, Ar*H*), 9.16 (1H, s, *H*–C=N), 9.58 (1H, s, N*H*). MS *m/z*: 353 $[M+H]^+$, 355 $[M+H+2]^+$.

(2Z,4Z)-9-Chloro-N-(2-fluorophenyl)-10-methyl-[1,3,4] thiadiazepino[7,6-b]quinolin-2-amine ***(4b)*** Dark yellow solid; m.p. 150 °C. FT-IR (KBr) cm^{-1}: 3,463 (N–H), 1,601 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.80 (3H, s, ArCH_3), 7.54 (1H, s, Ar*H*), 7.55 (1H, s, Ar*H*), 7.63–7.70 (3H, m, Ar*H*), 8.35 (1H, s, Ar*H*), 8.62 (1H, s, Ar*H*), 9.37 (1H, s, *H*–C=N), 9.78 (1H, s, N*H*). MS *m/z*: 371 $[M+H]^+$, 373 $[M+H+2]^+$.

(2Z,4Z)-9-Chloro-N-(3-fluorophenyl)-10-methyl-[1,3,4] thiadiazepino[7,6-b]quinolin-2-amine ***(4c)*** Dark yellow solid; m.p. 198 °C. IR (KBr) cm^{-1}: 3,430 (N–H), 1,604 (C=N), C–S (1,383). ^1H NMR: ($CDCl_3$) δ: 2.81 (3H, s, ArCH_3), 7.32–7.41 (2H, m, Ar*H*), 7.56 (1H, d, $J = 8.8$ Hz, Ar*H*), 7.67 (2H, d, $J = 8.0$ Hz, Ar*H*), 8.33 (1H, s, Ar*H*), 8.60 (1H, s, Ar*H*), 9.19 (1H, s, *H*–C=N), 9.60 (1H, s, N*H*). MS *m/z*: 371 $[M+H]^+$, 373 $[M+H+2]^+$.

(2Z,4Z)-9-Chloro-N-(4-fluorophenyl)-10-methyl-[1,3,4] thiadiazepino[7,6-b]quinolin-2-amine ***(4d)*** Yellow solid; m.p. 190 °C. IR (KBr) cm^{-1}: 3,415 (N–H), 1,638 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.80 (3H, s, ArCH_3), 7.10 (2H, t, $J = 8.8$ Hz, Ar*H*), 7.54–7.58 (2H, m, Ar*H*), 7.65 (1H, d, $J = 8.8$ Hz, Ar*H*), 8.34 (1H, s, Ar*H*), 8.60 (1H, s, Ar*H*), 9.07 (1H, s, *H*–C=N), 9.77 (1H, s, N*H*). MS *m/z*: 371 $[M+H]^+$, 373 $[M+H+2]^+$.

(2Z,4Z)-9-Chloro-N-(2-chlorophenyl)-10-methyl-[1,3,4] thiadiazepino[7,6-b]quinolin-2-amine ***(4e)*** Dark yellow solid; m.p. 120 °C. IR (KBr) cm^{-1}: 3,419 (N–H), 1,629 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.80 (3H, s, ArCH_3), 7.32–8.00 (5H, m, Ar*H*), 8.36 (1H, s, Ar*H*), 8.76 (1H, s, Ar*H*), 9.73 (1H, s, *H*–C=N), 9.80 (1H, s, N*H*). MS *m/z*: 387 $[M+H]^+$, 389 $[M+H+2]^+$, 391 $[M+H+4]^+$.

(2Z,4Z)-9-Chloro-N-(3-chlorophenyl)-10-methyl-[1,3,4] thiadiazepino[7,6-b]quinolin-2-amine ***(4f)*** Yellowish brown solid; m.p. 170 °C. IR (KBr) cm^{-1}: 3,480 (N–H), 1,610 (C=N), 1,384 (C–S). ^1H NMR ($CDCl_3$) δ: 2.80 (3H, s, ArCH_3), 7.41–7.73 (4H, m, Ar*H*), 8.00 (1H, s, Ar*H*),8.37 (1H, s, Ar*H*), 8.60 (1H, s, Ar*H*), 8.96 (1H, s, *H*–C=N), 9.80 (1H, s, N*H*). MS *m/z*: 386.9 $[M+H]^+$, 389 $[M+H+2]^+$, 391 $[M+H+4]^+$.

(2Z,4Z)-9-Chloro-N-(4-chlorophenyl)-10-methyl-[1,3,4] thiadiazepino[7,6-b]quinolin-2-amine ***(4g)*** Yellow solid; m.p. 116 °C. IR (KBr) cm^{-1}: 3,437 (N–H), 1,617 (C=N), 1,384 (C–S). ^1H NMR: ($CDCl_3$) δ: 2.86 (3H, s, ArCH_3), 7.37 (2H, d, $J = 8.8$ Hz, Ar*H*), 7.56 (1H, d,$J = 8.8$ Hz, Ar*H*), 7.62 (2H, d, $J = 8.8$ Hz, Ar*H*), 8.33 (1H, s, Ar*H*), 8.60 (1H, s, Ar*H*), 9.11 (1H, s, *H*–C=N), 9.61 (1H, s, N*H*). MS *m/z*: 387 ($[M+H]^+$, 12), 389 $[M+H+2]^+$, 391 $[M+H+4]^+$.

(2Z,4Z)-9-Chloro-10-methyl-N-o-tolyl-[1,3,4]thiadiazepino [7,6-b]quinolin-2-amine ***(4h)*** Yellow solid; m.p. 190 °C. IR (KBr) cm^{-1}: 3,425 (N–H), 1,611 (C=N), 1,384 (C–S). ^1H NMR: ($CDCl_3$) δ: 2.80 (3H, s, ArCH_3), 2.36 (3H, s, ArCH_3), 7.27 (2H, d, $J = 8.0$ Hz, Ar*H*), 7.54 (1H, d, $J = 8.8$ Hz, Ar*H*), 7.62 (2H, d, $J = 8.8$ Hz, Ar*H*), 8.35 (1H, s, Ar*H*), 8.58 (1H, s, Ar*H*), 8.96 (1H, s, *H*–C=N), 9.79 (1H, s, N*H*). MS *m/z*: 367 $[M+H]^+$, 369 $[M+H+2]^+$.

(2Z,4Z)-9-Chloro-10-methyl-N-p-tolyl-[1,3,4]thiadiazepi-no[7,6-b]quinolin-2-amine ***(4i)*** Yellow solid; m.p. 178 °C. IR (KBr) cm^{-1}: 3,490 (N–H), 1,640 (C=N), 1,384

(C–S). ^{1}H NMR: ($CDCl_3$) δ: 2.80 (3H, s, ArCH_3), 2.35 (3H, s, ArCH_3), 7.20 (1H, d, J = 8.4 Hz, ArH), 7.49 (2H, d, J = 7.6 Hz, ArH), 7.54 (1H, d, J = 8.8 Hz, ArH), 7.65 (1H, d, J = 8.8 Hz, ArH), 8.32 (1H, s, ArH), 8.60 (1H, s, ArH), 9.09 (1H, s, H–C=N), 9.73 (1H, s, NH). MS m/z: 367 $[M+H]^+$, 369 $[M+H+2]^+$.

*(2Z,4Z)-N-(2,6-Dimethylbenzyl)-9-chloro-10-methyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**4j**)* Light Yellow solid. m.p. 198 °C. IR (KBr) cm^{-1}: 3,490 (N–H), 1,636 (C=N), C–S (1,383). ^{1}H NMR ($CDCl_3$) δ: 2.81 (3H, s, ArCH_3), 2.32 (6H, s, ArCH_3), 7.14 (2H, d, J = 7.6 Hz, ArH), 7.54 (1H, d, J = 8.8 Hz, ArH), 7.62 (1H, d, J = 8.8 Hz, ArH), 8.33 (1H, s, ArH), 8.59 (1H, s, ArH), 8.68 (1H, s, H–C=N), 9.71 (1H, s, NH). MS m/z: 381 $[M+H]^+$, 383 $[M+H+2]^+$.

*(2Z,4Z)-N-(2,4-Dimethybenzyl)-9-chloro-10-methyl[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**4k**)* Light Yellow solid; m.p. 180 °C. IR (KBr) cm^{-1}: 3,488 (N–H), 1,611 (C=N), C–S (1,383). ^{1}H NMR ($CDCl_3$) δ: 2.81 (3H, s, ArCH_3), 2.31 (6H, s, ArCH_3), 7.42 (1H, d, J = 7.2 Hz, ArH), 7.54 (2H, d, J = 8.8 Hz, ArH), 7.64 (1H, s, ArH), 8.31 (1H, s, ArH), 8.59 (1H, s, ArH), 8.86 (1H, s, H–C=N), 9.57 (1H, s, NH). MS m/z: 381 $[M+H]^+$, 383 $[M+H+2]^+$.

*(2Z,4Z)-9-Chloro-N-(4-ethylphenyl)-10-methyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**4l**)* Yellow solid; m.p. 110 °C. IR (KBr) cm^{-1}: 3,438 (N–H), 1,635 (C=N), 1,384 (C–S). ^{1}H NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 7.5 Hz, CH_3), 2.66 (2H, q, J = 7.5 Hz, CH_2), 2.83 (3H, s, ArCH_3), 7.22–7.24 (2H, m, ArH), 7.52–7.56 (2H, m, ArH), 7.65 (1H, d, J = 8.8 Hz, ArH), 8.30 (1H, s, ArH), 8.67 (1H, s, ArH), 9.10 (1H, s, H–C=N), 9.54 (1H, s, NH). MS m/z: 381 $[M+H]^+$, 383 $[M+H+2]^+$.

*(2Z,4Z)-9-Chloro-N-benzyl-10-methyl-[1,3,4]thiadiazepino[7,6-b]quinolin-2-amine (**4m**)* Light Yellow solid; m.p. 190 °C. IR (KBr) cm^{-1}: 3,453 (N–H), 1,612 (C=N), C–S (1,383). ^{1}H NMR ($CDCl_3$) δ: 2.79 (3H, s, ArCH_3), 4.99 (2H, d, J = 6 Hz, CH_2), 7.30–7.42 (4H, m, ArH), 7.52 (1H, d, J = 8.8 Hz, ArH), 7.60 (1H, d, J = 8.8 Hz, ArH), 7.72 (1H, s, ArH), 8.23 (1H, s, ArH), 8.50 (1H, s, H–C=N), 9.33 (1H, s, NH). MS m/z: 367 $[M+H]^+$, 369 $[M+H+2]^+$.

*(2Z,4Z)-9-Chloro-10-methyl-N-(2-morpholinoethyl)-[1,3,4]thiadiazepino[7,6-b]quinoline-2-amine (**4n**)* Light Yellow solid; m.p. 240 °C. IR (KBr) cm^{-1}: 3,485 (N–H), 1,662 (C=N), 1,384 (C–S). ^{1}H NMR ($CDCl_3$) δ: 2.61 (3H, s, ArCH_3), 2.80 (4H, s,CH_2), 2.68 (2H, t, J = 5.5 Hz, CH_2), 3.80 (6H, m, CH_2), 7.53–7.59 (2H, m, ArH), 8.18 (1H, s, ArH), 8.65 (1H, s, H–C=N), 9.17 (1H, s, NH). MS m/z: 390 $[M+H]^+$, 392 $[M+H+2]^+$.

In vitro anti-bacterial activity assay

The anti-bacterial assay of all the synthesized compounds was carried out by microdilution method (Hanel and Raether, 1988; Voet and Voet, 2004) against the human pathogenic bacteria. The bacterial suspensions were adjusted with sterile saline to a concentration of 1.0×10^5 colony forming unit (CFU)/ml. The inocula were prepared daily and stored at +4 °C until use. Dilutions of the inocula were cultured on solid medium to verify the absence of contamination and to check the validity of the inoculum. The MICs were determined using 5-ml test tubes. Compounds under investigation were dissolved in broth LB medium (100 ml) with bacterial inoculum (1.0×10^4 cfu per tube) to achieve the desired concentrations (1 mg/ml). All the test tubes were incubated for 24 h at 48 °C. The lowest concentrations without visible growth (at the binocular microscope) were defined as concentrations that completely inhibited bacterial growth (MICs). Chloramphenicol was used as a positive control, whereas DMSO was used as negative control (1 mg/ml).

In vitro anti-fungal assay

Anti-fungal screening of the newly synthesized compounds was carried out by microdilution technique (Hanel and Raether, 1988) against *T. reesei*, *A. flavus*, *A. alternata*, *A. niger*, and *D. australiensis*. The micromycetes were maintained on malt agar and the cultures were stored at 4 °C and sub-cultured once a month (Booth, 1971). The inocula were stored at 4 °C for further use. Dilutions of the inocula were cultured on solid malt agar to verify the absence of contamination and to check the validity of the inoculum. MIC determinations were performed by a serial dilution technique using 5-ml test tubes. The compounds investigated were dissolved in DMSO (1 mg/ml) and added in broth malt medium with inoculum. The tubes were incubated for 72 h at 28 °C. The lowest concentrations without visible growth (at the binocular microscope) were defined as MICs. DMSO was used as a negative control, while commercially available fungicide, mancozeb, was used as positive control (1–3,000 μg/ml).

Conclusion

Keeping in view, well-established anti-bacterial and anti-fungal properties of thiadiazepines, two rings viz. quinoline and thiadiazepine were fused and four series of new (2Z,4Z)-9-chloro-10-methyl/8-methyl/10-methyl/8-methoxy-*N*-aryl/alkyl-[1,3,4]thiadiazepino[7,6-*b*]quinolin-2-amines (**1a**–**n**, **2a**–**n**, **3a**–**n**, and **4a**–**n**) were synthesized by conventional procedure as well as under the influence

of microwaves. All the compounds were assayed in vitro for the evaluation of their anti-microbial activity. Most of the compounds exhibited better anti-bacterial than anti-fungal activity against the microorganisms employed in this study. Furthermore, it revealed that the compounds obtained by the synergism could be useful as a template for further development through modification or derivatization to design more potent biologically active compounds. Facilitation of the syntheses with microwaves was found quite useful to obtain higher yields and purity compared to conventional refluxing and duration of reaction was reduced considerably to 1–2 min.

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