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Design, Synthesis and Screening of Quinoline-Incorporated Thiadiazole as a Potential Anticonvulsant

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A series of quinoline-incorporated substituted thiadiazole were designed and synthesized using appropriate synthetic route keeping in view the structural requirement of pharmacophore and evaluated for anticonvulsant and CNS activities. After intraperitoneal injection to mice, some synthesized derivatives were examined in the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazol (scPTZ)-induced seizure and neurotoxicity screens. Those found potent were also evaluated for behavioural impairment and depression activity. Among the compounds tested, 6d and 6e showed protection from seizures in both the animal models at dose level of 30 mg/kg while 7f showed protection against both models at 100 mg/kg dose level. These compounds exhibited lesser CNS depression and neurotoxicity compared with clinically effective drug.

Key words: anticonvulsant, behavioural test, neurotoxicity, quinoline, thiadiazole

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Epilepsy is one of the more common neurological disorders, affecting a large section of people (1). About 20–30% of patients have seizures that are resistant to available medical therapies. All currently approved antiepileptic drugs have dose-related toxicity and idiosyncratic side effects (2). Therefore, the search for a novel, highly effective and more selective agent with lesser side effects continues to be an area of investigation of medicinal chemist's world wide. Previously, we have reported several nitrogen-containing heterocyclic compounds based on the pharmacophoric pattern in terms of interaction at the binding site (3–5), and the results were encouraging enough to prompt us for further synthesizing more derivatives and test them against the convulsant stimuli. As quinolines have been recognized earlier as promising nuclei, with few of its derivatives have been synthesized and tested for their anticonvulsant activity (6–10). Different aryl and heteroaryl moieties have been clubbed to the quinoline pharmacophore as hydrophobic domain which led to the increase in the activity significantly. In this work, we planned to attach the quinoline to the substituted thiadiazole which has been observed to exhibit anticonvulsant properties in experimentally maximal electroshock seizure (MES) convulsions, as reported in previous screening data for anticonvulsant activity (11–17). Adding, these two active anticonvulsant moieties were expected to have synergistic effect in dealing with epilepsy.

All the synthesized titled compounds were comprised of the essential pharmacophoric elements (Figure 1) that are necessary for good anticonvulsant activity as suggested by Unverferth *et al.* (18). The essential structural features that could be responsible for an interaction with the active site of voltage-gated sodium channels were a hydrophobic HP unit (R), an electron donor (D) group and a hydrogen donor/acceptor (HBD) unit.

Experimental

Chemistry

Melting points were determined by the open capillary method with electrical melting point apparatus and are uncorrected. IR spectra were recorded as KBr (pallet) on Bio Rad FT-IR spectrophotometer and ^{1}H and ^{13}C-NMR spectra recorded on Bruker DPX 300 MHz spectrophotometer using DMSO-d_6 or $CDCl_3$ as a NMR solvent. TMS used as an internal standard and chemical shift data are reported in parts per million (in ppm) where s, bs, d, t and m designated as singlet, broad singlet, doublet, triplet and multiplet, respectively. Mass spectra were recorded on JEOL SX102/DA-6000

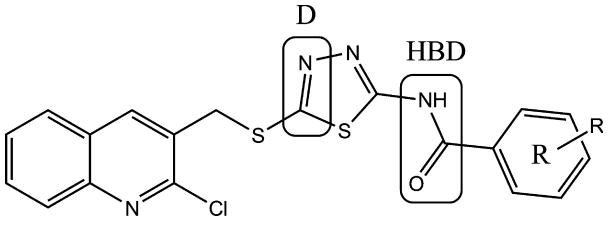


Figure 1: The essential structure elements for the pharmacophore of Unverferth *et al.* are indicated by rectangles.

mass spectrometer using *m*-nitrobenzylalcohol as a matrix and elemental analysis on Vario-EL III CHNOS-Elemantar analyzer. Thin-layer chromatography (TLC) was performed to monitor the progress of the reaction and purity of the compounds, spot being located under iodine vapour or UV-light.

Synthesis of 5-Sulfanyl-1,3,4-thiadiazol-2-ylamine (19) 1

A mixture of potassium hydroxide (5.34 mmol) and carbon disulphide (5.52 mmol) was dissolved in anhydrous ethanol (15 mL), later followed by addition of thiosemicarbazide (5.49 mmol) dissolved in anhydrous ethanol; the reaction mixture was stirred and heated to reflux for 8 h, the ethanol was removed by evaporation in vacuum, and the residue was dissolved in water (50 mL). This was slowly acidified with 5 mL of concentrated HCl. The precipitate was further filtered to produce compound. The crude product was washed with cold water, and this yellow solid so obtained was further recrystallized from ethyl acetate to give white solid.

Yield, 68%; m.p. 225 °C, IR (KBr)/cm: 3403, 3280, 3088, 2921, 1605, 1527, 1495, 1368, 1327, 1057; ^{1}H-NMR (300 MHz, DMSO-d_6): 6.4 (s, 2H, NH_2), 12.99 (s, 1H, NH).

2-Chloro-3-formylquinoline 2 needed in the study was also prepared previously by Vilsmeier–Haack reaction as reported in literature by our team (5)

Yield, 63.0%; m.p. 150–151 °C; IR (KBr)/cm: 1693 (C=O), 1620 (C=N), 1595 (C=C), 752 (C–Cl); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.67 (t, 1H, H-6, J = 7.4 Hz), 7.90 (t, 1H, H-7, J = 7.1 Hz), 8.01 (d, 1H, H-5, J = 8.0 Hz), 8.09 (d,1H, H-8, J = 8.4 Hz), 8.78 (s, 1H, H-4), 10.58 (s, 1H, CHO); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 125.9, 126.1, 127.3, 127.7, 129.6, 133.3, 135.0, 140.9, 148.2, 188.7 (CHO). FAB-MS: m/z 192 (M^+), 194 (M + 2).

Synthesis of 2-Chloro-3-(hydroxymethyl)-quinoline (20) 3

To a solution of 2-chloro-3-formylquinoline 1.92 g (0.01 mol) in absolute methanol, solid sodium borohydride 0.46 g (0.012 mol) was added portionwise over a period of 30 min with constant stirring at room temperature. After, that solvent was evaporated under reduced pressure and the residue was triturated with water to yield crystalline product which was filtered, washed with water and dried. The crude product was further recrystallized from methanol. Yield, 86.0%; m.p. 160–162 °C.

IR (KBr)/cm: 3340 (O–H), 1614 (C=N), 1592 (C=C), 765 (C–Cl); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 4.77 (s, 2H, CH_2), 5.45 (s, 1H, OH, D_2O-exchangeable), 7.55 (t, 1H, H-6, J = 7.0 Hz), 7.70 (t, 1H, H-7, J = 6.9 Hz), 7.84 (d, 1H, H-5, J = 7.5 Hz), 7.99 (d,1H, H-8, J = 8.0 Hz), 8.36 (s, 1H, H-4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 59.9 (CH_2), 126.4, 127.0, 127.4, 127.7, 129.9, 133.8, 135.7, 146.0, 148.3; FAB-MS: m/z 194 (M^+), 196 (M + 2).

Synthesis of 3-(Chloromethyl)-2-chloroquinoline (20) 4

To a solution of compound **3** 1.94 g (0.01 mol) in dry benzene, $SOCl_2$ 1.54 g (0.013 mol) was added and the mixture refluxed for 4 h. Solvent was evaporated under reduced pressure, and the residue so obtained was further dissolved in ether, washed with 10% $NaHCO_3$, followed by washing twice with water, and dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a residue which was crystallized from methanol. Yield 80%; m.p. 116 °C.

IR (KBr)/cm: 1620 (C=N), 1590 (C=C), 754 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.82 (s, 2H, CH_2), 7.56 (t, 1H, H-6, J = 7.2 Hz), 7.73 (t, 1H, H-7, J = 7.5 Hz), 7.82 (d, 1H, H-5, J = 7.9 Hz), 8.01 (d,1H, H-8, J = 8.3 Hz), 8.26 (s, 1H, H-4); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 43.03 (CH_2), 126.9, 127.3, 127.4, 128.1, 128.8, 130.8, 138.6, 147.1, 149.5; FAB-MS : m/z 212 (M^+), 214 (M + 2).

Synthesis of 5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-amine (21) 5

5-Sulfanyl-1,3,4-thiadiazol-2-ylamine (0.1 mol) was suspended in water (9 mL), and 0.1 mol of KOH (85% solution) was added under stirring at room temperature. After a few minutes, the solution was brought to 0 °C in an ice bath, and 3-(chloromethyl)-2-chloroquinoline (0.1 mol) was dropped in with vigorous stirring. The reaction mixture was monitored by TLC. When the reaction completed, water (30 mL) was added, and from the crude mixture, a precipitate of **5** formed out slowly which was filtered, washed with water and crystallized. Yield 67%; m.p. 194 °C.

IR (KBr)/cm: 3352 (N–H), 1613 (C=N), 1587 (C=C), 754 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.59 (s, 2H, SCH_2), 6.82 (s, 2H, NH_2), 7.57, (t, 1H, H-6, J = 7.5 Hz), 7.71 (t, 1H, H-7, J = 7.2 Hz), 7.82 (d, 1H, H-5, J = 7.9 Hz), 8.02 (d,1H, H-8, J = 8.1 Hz), 8.19 (s, 1H, H-4); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 36.03 (CH_2), 117.6, 126.8, 127.8, 129.5, 131.9, 132.6, 142.9, 145.7, 146.7, 168.8; FAB-MS : m/z 309 (M^+), 311 (M + 2).

General procedure for synthesis of compounds (22) (6a–e)

To compound **5** which was suspended in a slight excess of 10% w/v sodium hydroxide solution, a small excess of acid chloride (**a**–**e**) was then added in a portionwise and the mixture was vigorously shaken in a stoppered conical flask. This facilitated acylation which yield sparingly soluble acylated crude derivatives, which was separated as a solid, further washed and recrystallized. The physicochemical data of the synthesized derivatives are summarized in Table 1.

N-{5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-yl)acetamide 6a IR (KBr)/cm: 3408 (N–H), 1666 (C=O), 1604 (C=N), 1590 (C=C), 757 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, $COCH_3$), 4.54 (s, 2H, SCH_2), 7.53, (t, 1H, H-6, J = 7.8 Hz), 7.73 (t, 1H, H-7, J = 7.2 Hz), 7.81 (d, 1H, H-5, J = 8.1 Hz), 8.04 (d,1H, H-8, J = 8.1 Hz), 8.21 (s, 1H, H-4), 11.47 (bs, 1H, CONH); ^{13}C-NMR

Table 1: Physicochemical data of synthesized final compounds

Compound No.	R/R[1]	Yield[a] (%)	m.p. (°C)	Mol. formula[b]	Mol. wt
6a	CH_3	71	208–210	$C_{14}H_{11}ClN_4OS_2$	350.84
6b	CH_2CH_3	68	216–218	$C_{15}H_{13}ClN_4OS_2$	364.87
6c	C_6H_5	73	220–221	$C_{19}H_{13}ClN_4OS_2$	412.91
6d	*p*-CH_3–C_6H_4	64	214–215	$C_{20}H_{15}ClN_4OS_2$	426.93
6e	*p*-Cl–C_6H_4	67	225–226	$C_{19}H_{12}Cl_2N_4OS_2$	447.35
7a	CH_3	60	204–205	$C_{14}H_{11}ClN_4S_2$	334.84
7b	C_6H_5	63	207–209	$C_{19}H_{13}ClN_4S_2$	396.91
7c	*p*-CH_3–C_6H_4–	59	210–212	$C_{20}H_{15}ClN_4S_2$	410.94
7d	*p*-OCH_3–C_6H_4–	73	211–216	$C_{20}H_{15}ClN_4OS_2$	426.94
7e	*p*-Cl–C_6H_4–	55	215–219	$C_{19}H_{12}Cl_2N_4S_2$	431.36
7f	*p*-F–C_6H_4–	51	222–226	$C_{19}H_{12}ClFN_4S_2$	414.90
7g	*p*-NO_2–C_6H_4–	73	225–228	$C_{19}H_{12}ClN_5O_2S_2$	441.91
8a	CH_3	57	209–211	$C_{14}H_{13}ClN_4S_2$	336.84
8b	C_6H_5	60	213–218	$C_{19}H_{15}ClN_4S_2$	398.91
8c	*p*-CH_3–C_6H_4–	55	215–219	$C_{20}H_{17}ClN_4S_2$	412.95
8d	*p*-OCH_3–C_6H_4–	50	216–218	$C_{20}H_{17}ClN_4OS_2$	428.95
8e	*p*-Cl–C_6H_4–	62	221–223	$C_{19}H_{14}Cl_2N_4S_2$	433.37
8f	*p*-F–C_6H_4–	49	222–224	$C_{19}H_{14}ClFN_4S_2$	416.91
8g	*p*-NO_2–C_6H_4–	45	227–229	$C_{19}H_{14}ClN_5O_2S_2$	443.92

[a]Recrystallization from ethanol; [b]Elemental analyses for C, N were within ± 0.4% of the theoretical values.

($CDCl_3$, 75 MHz): δ 22.8 (CH_3), 36.6, (CH_2), 117.8, 125.4, 126.5, 128.8, 129.0, 129.9, 130.7, 131.8, 132.6, 140.7, 145.9, 146.8, 166.3, 171.2; FAB-MS : *m/z* 351 (M^+), 353 (M + 2).

N-(5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-yl)propanamide 6b IR (KBr)/cm: 3409 (N–H), 1673 (C=O), 1611 (C=N), 1576 (C=C), 754 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.02 (t, 3H, CH_3), 2.31 (m, 2H, $COCH_2$), 4.56 (s, 2H, SCH_2), 7.50 (t, 1H, H-6, *J* = 7.3 Hz), 7.75 (t, 1H, H-7, *J* = 7.0 Hz), 7.79 (d, 1H, H-5, *J* = 8.4 Hz), 8.10 (d,1H, H-8, *J* = 8.1 Hz), 8.24 (s, 1H, H-4), 12.08 (bs, 1H, CONH).

N-(5-{[(2-chloroquinolin-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-yl)benzamide 6c IR (KBr)/cm: 3387 (N–H), 1663 (C=O), 1609 (C=N), 1577 (C=C), 761 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.58 (s, 2H, SCH_2), 7.53–7.65 (m, 4H, Ar-H & H-6), 7.78–7.86 (m, 4H, Ar-H & H-5, H-7), 8.14 (d,1H, H-8, *J* = 7.8 Hz), 8.21 (s, 1H, H-4), 11.51 (s, 1H, CONH); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 35.3, (CH_2), 115.9, 125.6, 126.4, 127.3, 127.9, 128.6, 129.3, 129.9, 130.7, 131.6, 132.5, 136.8, 140.5, 146.3, 147.2, 165.8, 170.4.

N-(5-{[(2-chloroquinolin-3-yl)methyl]thio}-1,3,4-thiadiazol-2-yl)-4-methylbenzamide 6d IR (KBr)/cm: 3392 (N–H), 1677 (C=O), 1615 (C=N), 1593 (C=C), 762 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 4.54 (s, 2H, SCH_2), 7.29 (d, 2H, Ar-H, J = 7.4 Hz), 7.56 (t, 1H, H-6, J = 7.4 Hz), 7.77–7.84 (m, 4H, Ar-H, H-5 and H-7), 8.11 (d,1H, H-8, *J* = 7.5 Hz), 8.19 (s, 1H, H-4), 11.96 (bs, 1H, CONH). FAB-MS : *m/z* 426 (M^+), 427 (M + 1), 428 (M + 2).

4-Chloro-N-(5-{[(2-chloroquinolin-3-yl)methyl]thio}-1,3,4-thiadiazol-2-yl)benzamide 6e IR (KBr)/cm: 3385 (N–H), 1668 (C=O), 1612 (C=N), 1596 (C=C), 759 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.57 (s, 2H, SCH_2), 7.54 (t, 1H, H-6, J = 7.1 Hz), 7.67–7.83 (m, 6H, Ar-H & H-5, H-7), 8.09 (d,1H, H-8, *J* = 7.3 Hz), 8.22 (s, 1H, H-4), 11.39 (s, 1H, CONH).

General procedure for the synthesis of compounds (23) (7a–g)

To a solution of compound **5** (0.01 mol) in 30 mL of absolute ethanol, an equimolar amount of substituted carbaldehyde (**a**–**g**) (0.01 mol) and 3 mL of glacial acetic acid were added. The content of the flask was refluxed for 6–8 h. The progress of the reaction was monitored on TLC, and on completion of the reaction, content of the flask was reduced to one-third and poured in ice water after which the pH of the solution was adjusted to neutral with dil. $NaHCO_3$ solution, and the precipitate thus formed was filtered off, washed with cold aqueous ethanol, dried and crystallized from ethanol to give the compound **7a**–**g**. The physicochemical data of synthesized were presented in Table 1.

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-(ethyl-2-ylidene)-1,3,4-thiadiazol-2-amine 7a IR (KBr)/cm: 1611 (C=N), 1583, (C=C), 763 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.16 (d, 3H, CH_3,), 4.57 (s, 2H, SCH_2), 7.49 (t, 1H, H-6, *J* = 7.3 Hz), 7.79 (t, 1H, H-7, *J* = 7.2 Hz), 7.76 (d, 1H, H-5,), 8.08 (d,1H, H-8, *J* = 7.8 Hz), 8.18 (s, 1H, H-4), 8.51 (m, 1H, CH=N); FAB-MS : *m/z* 335 (M^+), 337 (M + 2).

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-[-phenylmethylidene]-1,3,4-thiadiazol-2-amine 7b IR (KBr)/cm: 1609 (C=N), 1576, (C=C), 765 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.61 (s, 2H, SCH_2), 7.45–7.64 (m, 4H, Ar-H & H-6), 7.72 (t, 1H, H-7, *J* = 7.2 Hz), 7.79–7.86 (m, 3H, Ar-H & H-5), 8.05 (d,1H, H-8, *J* = 7.8 Hz), 8.15 (s, 1H, H-4), 8.78 (s, 1H, CH=N); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 34.9, (CH_2), 117.2, 126.4, 127.3, 128.0, 128.8, 129.5, 129.9, 131.9, 132.6, 135.0, 141.7, 146.1, 147.4, 157.9, 165.7; FAB-MS : *m/z* 397(M^+), 399 (M + 2).

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-[-(4-methylphenyl)methylidene]-1,3,4-thiadiazol-2-amine 7c IR (KBr)/cm: 1605 (C=N), 1579, (C=C), 768 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.37, (s, 3H, CH_3),

4.58 (s, 2H, SCH_2), 7.13 (d, 2H, Ar-H, J = 7.6 Hz), 7.49 (t, 1H, H-6, J = 7.8 Hz), 7.69 (t, 1H, H-7, J = 7.8 Hz), 7.73–7.81 (m, 3H, Ar-H & H-5), 8.08 (d,1H, H-8, J = 7.5 Hz), 8.14 (s, 1H, H-4), 8.89 (s, 1H, CH=N).

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-[-(4-methoxyphenyl)methylidene]-1,3,4-thiadiazol-2-amine 7d IR (KBr)/cm: 1610 (C=N), 1582, (C=C), 759 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.71, (s, 3H, OCH_3), 4.62 (s, 2H, SCH_2), 6.98 (d, 2H, Ar-H, J = 7.3), 7.34 (d, 2H, Ar-H, J = 7.1), 7.52 (t, 1H, H-6, J = 7.0 Hz), 7.74 (t, 1H, H-7, J = 7.5 Hz), 7.81 (d, 1H, H-5, J = 7.7 Hz), 8.10 (d,1H, H-8, J = 7.5 Hz), 8.18 (s, 1H, H-4), 8.79 (s, 1H, CH=N); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 34.8, (CH_2), 113.8, 118.0, 126.2, 128.7, 129.3, 129.8, 130.4, 131.6, 132.4, 133.5, 136.3, 141.4, 144.8, 146.1, 156.7, 161.8, 167.2.

N-[-(4-Chlorophenyl)methylidene]-5-{[(2-chloroquinolin-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-amine 7e IR (KBr)/cm: 1603 (C=N), 1561, (C=C), 755 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.59 (s, 2H, SCH_2), 7.51–7.58 (m, 3H, Ar-H & H-6), 7.71 (t, 1H, H-7, J = 7.4 Hz), 7.75–7.81 (m, 3H, Ar-H & H-5), 8.05 (d,1H, H-8, J = 7.6 Hz), 8.16 (s, 1H, H-4), 8.82 (s, 1H, CH=N).

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-[-(4-fluorophenyl)methylidene]-1,3,4-thiadiazol-2-amine 7f IR (KBr)/cm: 1607 (C=N), 1582, (C=C), 763 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.57 (s, 2H, SCH_2), 7.51–7.59 (m, 3H, Ar-H and H-6), 7.73 (t, 1H, H-7, J = 7.0 Hz), 7.80–7.86 (m, 3H, Ar-H & H-5), 8.09 (d,1H, H-8, J = 7.0 Hz), 8.18 (s, 1H, H-4), 8.80 (s, 1H, CH=N).

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-[-(4-nitrophenyl)methylidene]-1,3,4-thiadiazol-2-amine 7g IR (KBr)/cm: 1614 (C=N), 1553, (C=C), 760 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.56 (s, 2H, SCH_2), 7.54–7.61 (m, 3H, Ar-H and H-6), 7.73 (t, 1H, H-7, J = 7.0 Hz), 7.80 (d, 1H, H-5, J = 7.0 Hz), 8.07–8.13 (m, 3H, Ar-H and H-8), 8.16 (s, 1H, H-4), 8.83 (s, 1H, CH=N).

General procedure for the synthesis of compounds (23) (8a–g)

To a solution of (**7a**–**g**) (0.01 mol) in absolute methanol (50 mL), solid sodium borohydride (0.015 mol, 0.46 g) was added portionwise over a period of 30 min with constant stirring at room temperature. After that, the content of the flask was refluxed for 4–6 h. The solvent was evaporated under reduced pressure, and the residue was triturated with water (25 mL), when the crystalline solid separated out which was filtered, washed with water and dried. The product was recrystallized from methanol to give colourless to cream coloured crystals. The physicochemical data of synthesized were presented in Table 1.

N-Ethyl-5-{[(2-methylquinolin-3-yl)methyl]thio}-1,3,4-thiadiazol-2-amine 8a IR (KBr)/cm: 3378 (N–H), 1608 (C=N), 1583 (C=C), 1034 (C–N), 770 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.16 (s, 2H, NCH_2), 3.41 (s, 1H, NH), 4.51 (s, 2H, SCH_2), 7.52 (t, 1H, H-6, J = 7.5 Hz), 7.77 (t, 1H, H-7, J = 7.3 Hz), 7.82 (d, 1H, H-5, J = 8.0 Hz), 8.08 (d, 1H, H-8, J = 7.6 Hz), 8.17 (s, 1H, H-4); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 15.4, 35.9, (CH_2), 41.5, 117.2, 126.6, 128.4, 129.2, 129.9, 130.8, 132.8, 141.3, 146.4, 147.7, 164.9. FAB-MS : m/z 337 (M^+), 339 (M + 2).

N-Benzyl-5-{[(2-chloroquinolin-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-amine 8b IR (KBr)/cm: 3375 (N–H), 1615 (C=N), 1590 (C=C), 1030 (C–N), 769 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.69 (bs, 1H, NH), 4.03 (d, 2H, NCH_2), 4.57 (s, 2H, SCH_2), 7.03 (d, 2H, Ar-H, J = 7.1 Hz), 7.34 (m, 3H, Ar-H), 7.54 (t, 1H, H-6, J = 7.6 Hz), 7.72 (t, 1H, H-7, J = 7.5 Hz), 7.82 (d, 1H, H-5, J = 7.4 Hz), 8.03 (d,1H, H-8, J = 7.8 Hz), 8.11 (s, 1H, H-4); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 36.4, (CH_2), 46.8, 116.8, 125.8, 126.4, 128.6, 129.1, 129.9, 130.5, 131.8, 133.2, 140.6, 142.5, 144.9, 146.5, 166.0; FAB-MS : m/z 399 (M^+), 401 (M + 2).

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-(4-methylbenzyl)-1,3,4-thiadiazol-2-amine 8c IR (KBr)/cm: 3381 (N–H), 1607 (C=N), 1593 (C=C), 1037 (C–N), 758 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.39, (s, 3H, CH_3), 3.60 (bs, 1H, NH), 3.95 (d, 2H, NCH_2), 4.56 (s, 2H, SCH_2), 7.10 (d, 2H, Ar-H, J = 7.1 Hz), 7.32 (d, 2H, Ar-H, J = 7.5 Hz), 7.51 (t, 1H, H-6, J = 7.1 Hz), 7.76 (t, 1H, H-7, J = 7.2 Hz), 7.79 (d, 1H, H-5, J = 7.8 Hz), 8.03 (d,1H, H-8, J = 7.5 Hz), 8.13 (s, 1H, H-4).

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-(4-methoxybenzyl)-1,3,4-thiadiazol-2-amine 8d IR (KBr)/cm: 3358 (N–H), 1611 (C=N), 1582 (C=C), 1032 (C–N), 761 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.58 (bs, 1H, NH), 3.79 (s, 3H, OCH_3), 4.06 (d, 2H, NCH_2), 4.61 (s, 2H, SCH_2), 7.03 (d, 2H, Ar-H, J = 7.2 Hz), 7.42 (d, 2H, Ar-H, J = 7.5 Hz), 7.51 (d, 1H, H-6, J = 7.5), 7.76 (t, 1H, H-7, J = 7.4 Hz), 7.82 (d, 1H, H-5, J = 7.8 Hz), 8.03 (d,1H, H-8, J = 7.0 Hz), 8.14 (s, 1H, H-4).

N-(4-Chlorobenzyl)-5-{[(2-chloroquinolin-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-amine 8e IR (KBr)/cm: 3368 (N–H), 1608 (C=N), 1591 (C=C), 1039 (C–N), 764 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.63 (bs, 1H, NH), 4.03 (d, 2H, NCH_2), 4.60 (s, 2H, SCH_2), 7.34–7.42 (m, 4H, Ar-H), 7.54 (t, 1H, H-6, J = 7.5 Hz), 7.75 (t, 1H, H-7, J = 7.3 Hz), 7.81 (d, 1H, H-5, J = 7.7 Hz), 8.05 (d,1H, H-8, J = 7.6 Hz), 8.14 (s, 1H, H-4).

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-(4-fluorobenzyl)-1,3,4-thiadiazol-2-amine 8f IR (KBr)/cm: 3375 (N–H), 1613 (C=N), 1580 (C=C), 1028 (C–N), 770 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.55 (bs, 1H, NH), 3.98 (d, 2H, NCH_2), 4.59 (s, 2H, SCH_2), 7.31 (d, 2H, Ar-H, J = 7.7 Hz), 7.53–7.60 (m, 3H, Ar-H and H-6), 7.74 (t, 1H, H-7, J = 7.0 Hz), 7.80 (d, 1H, H-5, J = 7.8 Hz), 8.03 (d,1H, H-8, J = 7.0 Hz), 8.12 (s, 1H, H-4).

5-{[(2-Chloroquinolin-3-yl)methyl]sulfanyl}-N-(4-nitrobenzyl)-1,3,4-thiadiazol-2-amine 8g IR (KBr)/cm: 3363 (N–H), 1613 (C=N), 1589 (C=C), 1031 (C–N), 758 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.65 (bs, 1H, NH), 4.04 (d, 2H, NCH_2), 4.54 (s, 2H, SCH_2), 7.41 (d, 2H, Ar-H, J = 7.7 Hz), 7.54 (d, 1H, H-6, J = 7.4), 7.74 (d, 1H, H-7, J = 7.6 Hz), 7.82–7.7.89 (m, 3H, Ar-H and H-5), 8.04 (d,1H, H-8, J = 7.0 Hz), 8.15 (s, 1H, H-4).

Table 2: Anticonvulsant and neurotoxicity screening of compounds. Evaluation of compounds in the mouse intraperitoneal maximal electroshock seizure (MES), scPTZ and NT screens[a]

	MES screen		PTZ screen		Neurotoxicity screen	
Compound No.	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
6b	100	100	100	300	–	300
6c	100	300	100	300	300	300
6d	30	100	30	100	–	300
6e	30	30	30	100	–	–
7b	100	300	300	300	300	300
7d	300	300	300	300	×	×
7f	100	100	100	300	–	300
7g	100	300	100	300	300	300
8b	300	300	300	300	×	×
8d	300	300	300	300	×	×
8e	300	300	300	300	×	×
8g	300	300	300	300	×	×
Phenytoin	30	30	×	×	100	100
Sodium Valporate	×	×	300	–	–	–

[a]Doses of 30, 100 and 300 mg/kg of the compound were administered and the protection and neurotoxicity measured after 0.5 and 4 h. The figures indicate the minimal dose required to cause protection or neurotoxicity in 50% or more of the animals. The dash (–) indicates the absence of anticonvulsant activity or neurotoxicity. × denotes not tested.

Pharmacology

The preliminary anticonvulsant evaluation was made using reported procedures (24–27). Male albino mice (18–25 g) were used as experimental animals. All the test compounds were suspended in 30% PEG. The animals were kept at 25 ± 2 °C, in the groups of six percentage receiving chow pellets and water. The light–dark cycle was 12 h:12 h. Efforts were made to avoid any unnecessary distress to the animals. All the animal tests have been performed in accordance with the institutional animal ethical committee approval.

Anticonvulsant screening

Anticonvulsant evaluations were undertaken using the reported procedures (24,28). Initially, all the test compounds were administered i.p. in a volume of 0.01 mL/g b.w. of mice at doses of 30, 100 and 300 mg/kg to 1–6 animals. Anticonvulsant activity was assessed after 0.5-h and 4-h intervals of administration. Activity was established using the MES and scPTZ tests, and data are summarized in Table 2.

Neurotoxicity screen

Rotarod test has been performed to detect the motor deficit in mice (25). Animals were divided in the groups of four animals and trained to stay on accelerating rotarod that rotates at 10 revolutions per minute. The rod diameter was 3.2 cm. Trained animals (able to stay on the rotarod for at least two consecutive periods of 90 s) were given an i.p. injection of the test compounds in the doses of 30, 100 and 300 mg/kg. Neurological deficit was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials. The dose at which animal fell off the rod was determined, and data are presented in Table 2.

Behavioural test

Some of the titled compounds (30 mg/kg) were screened for their behavioural effects using an actophotometer at 0.5 and 1 h after injection in each group of six animals (26). Animals were acclimatized to the dark environment 24 h before the test. The control administered was 30% PEG only. The behaviour of the animal inside the photocell was recorded as digital score. Increased score represented good behavioural activity (Table 3).

CNS depressant study

The forced swim pool method reported earlier by Porsolt *et al.* (27) was followed. Mice (six animals in each group) were placed in chamber (diameter 45 cm, height 20 cm) containing water up to the height of 15 cm at 25 ± 2 °C. Two swim sessions were conducted,

Table 3: Behavioural study on some selected compounds using actophotometer

		Posttreatment (locomotor activity score)[b]	
Compounds[a]	Activity score Control (24 h prior)	0.5 h after	1 h after
6d	327.17 ± 12.37	259.00 ± 13.37	294.50 ± 8.80
6e	289.00 ± 11.16	256.17 ± 21.48[NS]	275.50 ± 13.65
7f	143.33 ± 9.09	129.50 ± 14.33	150.17 ± 18.60[NS]
Phenytoin[c]	119.33 ± 17.43	78.87 ± 16.66	97.17 ± 13.49

[a]Compounds were tested at a dose level of 100 mg/kg (i.p.).
[b]Each score represents the mean ± SEM of six mice, significantly different from control at $p < 0.05$, and NS denote the value, which were not significant (student's *t*-test).
[c]Tested at a dose level of 30 mg/kg (i.p.).

Table 4: CNS study on selected compounds in a forced swim pool test

Compounds[a]	Immobility time (s)	
	Control[b] (24 h prior)	Posttreatment[c] (1h after)
Vehicle	160.00 ± 13.37	173.50 ± 11.54[NS]
6d	148.17 ± 7.89	145.83 ± 9.63
6e	139.53 ± 12.61	143.33 ± 4.57
7f	137.33 ± 10.83	158.50 ± 6.72
Carbamazepine[d]	143.33 ± 8.42	169.00 ± 11.63

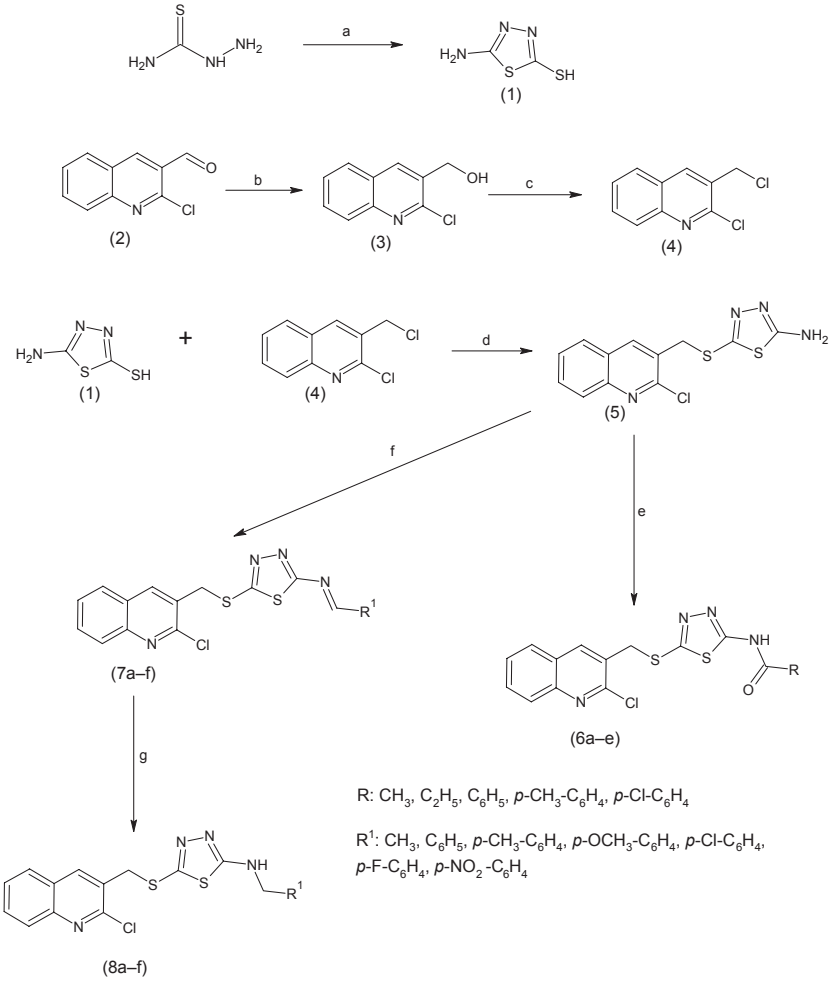
[a]Compounds were tested at a dose of 100 mg/kg (i.p.).
[b]Control animals were administered PEG (i.p.).
[c]Each value represents the mean ± SEM of six mice significantly different from the control at $p < 0.05$ (NS – not significant).
[d]Tested at 30 mg/kg (i.p.).

an initial 15 min pretest, followed by a 5-min test session 24 h later. The animals were administered an i.p. injection (30 mg/kg) of the test compound 30 min before the test session. The period of immobility (passive floating without struggling, making only those movements which were necessary to keep its head above the surface) during the 5 min test period was measured. This immobility reflected state of depression. Carbamazepine was used as a reference for comparison at a dose of 30 mg/kg (i.p., in PEG). The control animals were administered 30% PEG (Table 4).

Results and Discussion

Chemistry

The reaction sequence for the synthesis of compounds (**6a**–**e**, **7a**–**g** and **8a**–**g**) is outlined in Scheme 1. The required penultimate intermediate **5** that was prepared in moderate yield from reported 2-chloro-3-formyl quinoline **2** *via* its reduction with solid $NaBH_4$ in methanol to afford 2-chloro-3-hydroxymethyl quinoline **3**, followed by chlorination with $SOCl_2$ in dry benzene gave 3-(chloromethyl)-2-chloroquinoline **4**, which on subsequent reaction with 5-sulfanyl-1,3,4-thiadiazol-2-ylamine gave compound **5**. The target compounds



Scheme 1: Synthetic pathway of the targeted compounds **6a**–**e**, **7a**–**g** and **8a**–**g**. Reagents and conditions: (a) KOH/CS_2 in ethanol, r.t 8 h; (b) $NaBH_4$ portionwise, stirring 30 min; (c) $SOCl_2$, reflux for 4 h; (d) KOH (85% solution), stirring at 0 °C in an ice bath; (e) substituted acid chloride in 10% w/v NaOH solution; (f) substituted carbaldehyde and glacial acetic acid, reflux 6–8 h; (g) $NaBH_4$ portionwise, stirring 30 min, then reflux 4–6 h.

(**6a**–**e**, **7a**–**g** and **8a**–**g**) were obtained in moderate to good yield by following different reaction pathways (Scheme 1 and Table 1). Both analytical and spectral data (IR, ^{1}H & ^{13}C-NMR and Mass) of all the synthesized compounds were in full agreement with the proposed structures. In the IR spectra of compounds (**6a**–**e**), the band representing N–H and CO of –NHCO– appeared at 3385–3409 and 1663–1677/cm, respectively. In ^{1}H-NMR spectra of compounds (**6a**–**e**), the characteristics peak of-NHCO– was observed as singlet to broad singlet at δ 11.39–12.08 ppm equivalent to one proton of NH, while in ^{13}C-NMR spectra, the carbonyl carbon of –NHCO– was resonated at δ 171.2 in compound **6a**. In ^{1}H-NMR spectra of compounds (**7a**–**g**), the azomethine proton was appeared as singlet integrating for one proton at δ value ranging 8.51–8.89 ppm. The transformation of azomethines (**7a**–**g**) into secondary amines was accomplished using $NaBH_4$, and characteristic methylene amine function was identified by ^{1}H-NMR in which two new signals at δ value ranging from 3.41–3.69 to 2.16–4.06 arises owing to –NH and $-CH_2-$ function, respectively. The disappearance of azomethine group also supported the fact. Furthermore, in ^{13}C-NMR spectra, $-NHCH_2$ carbon of compound **8a** and **8b** was observed at δ 35.9 and 36.4 respectively. This is considered to be a strong confirmation for the synthesis of compounds (**8a**–**g**). The confirmation of synthesis of compounds was also supported by the FAB-MS spectrometry of some selected compounds **6a**, **6d**, **7a**, **7b** and **8a**, which registered molecular ion peak at *m/z* 351, 426, 335, 397 and 337 respectively. The spectral details of individual compound have been given in experimental section.

Pharmacology

Some of the new derivatives obtained by the above-mentioned procedure were undertaken for the initial anticonvulsant studies by the anticonvulsant drug development (ADD) programme protocol (28). The profile of anticonvulsant activity was established after i.p. injections into mice and evaluated in the MES, subcutaneous pentylenetetrazole (scPTZ) and neurotoxicity screens, using doses of 30, 100 and 300 mg/kg at two different time intervals. These data are presented in Table 2. Those found potent on initial preliminary screening were evaluated for their CNS behavioural activity in mice using actophotometer and CNS depressant study using Porsolt's forced swim pool test. The results are presented in Tables 3 and 4, respectively.

Anticonvulsant activity

All the tested compounds showed protection against MES test indicative of their ability to inhibit the seizure spread. Compounds **6d** and **6e** showed protection against the MES model at 30 mg/kg while some compounds **6b**, **6c**, **7b**, **7f** and **7g** showed protection at dose level of 100 mg/kg. The compound **6e** showed activity at both 0.5- and 4-h period at dose level of 30 mg/kg indicating the compound to be highly potent and long acting. Similarly compound **6d** was also found to be highly potent but short acting as 4-h protection requires the dose of 100 mg/kg. The compounds **6b** and **7f** showed activity both at 0.5- and 4-h period at dose level of 100 mg/kg, indicating that the compounds are potent and long acting while compounds **6c**, **7b** and **7g** showed activity only at 0.5 h at 100 mg/kg dose, indicating that these are having rapid onset and shorter duration of action.

All the tested compounds of this series were found to be active in the scPTZ test, a test used to identify compounds that elevate seizure threshold. Compounds **6d** and **6e** showed activity at a dose of 30 mg/kg while **6b**, **6c**, **7f** and **7g** showed activity at dose of 100 mg/kg, Among the tested compounds, **6d** and **6e** were found to be highly potent having rapid onset but with intermediate duration of action. Compounds **6b**, **6c**, **7f** and **7g** were found to be having rapid onset and short duration of action as these derivatives are effective at 0.5-h interval but required higher dose to be effective at 4 h. While the rest of compounds were found to had low potency and short duration of action.

Two general trends may be discerned. First, data for the MES and scPTZ tests revealed that 33% and 50%, respectively, of the compounds had greater activity at the end of 0.5 h than after 4 h. Thus, in general, these compounds are short-acting anticonvulsant. Secondly, protection was afforded by all the tested compounds in the MES and scPTZ screen, respectively. No compound showed greater activity in the scPTZ screen rather than MES test, while **6e** showed better activity in the MES model.

In neurotoxicity screen, compound **6e** did not show neurotoxicity in the maximum administered dose (300 mg/kg), and the remaining compounds were found to be less neurotoxic as compared to phenytoin.

In the behavioural study, using actophotometer, the compounds **6e** and **7f** showed no behavioural despair effect when compared to phenytoin as represented in Table 3. Compound **6d** showed decreased locomotor activity in the 0.5-h interval but no significant effect on behavioural despair was observed during 1-h time period. Similarly, results obtained in Porsolt's swim pool test with compound **7f**, in which an increase in the slight immobility time by the compounds indicated the CNS depressant effect. Rest of the tested compounds showed no significant variation from control.

Conclusion

As observed through data analysis, the compounds with amido linkage are more potent than having azomethine linkage which in turn better than substituted amino derivative as can be observed that none of **8a**–**g** does not produced fruitful result, so this might be due to involvement and binding of certain groups on thiadiazole with the receptor site, so probably amido derivate (**6a**–**e**) that are most potent might be playing role in hydrogen bonding, i.e., interaction with receptor site; thus, pharmacophoric features that are essential for a ligand to interact with receptor site to elicit action were achieved through the presence of amido group in designed molecules.

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Conflict of Interest

The authors declared that there are no conflicts of interest.

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