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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Molecular sieves promoted, ultrasound-mediated synthesis, biological evaluation and docking study of 3-(5-substituted-1,3,4-thiadiazol-2-ylimino)indolin-2-ones as a potential anticonvulsant agents

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**Abstract** In this work, the combined use of ultrasonic energy and molecular sieves was investigated for synthesis of 3-(5-substituted-1,3,4-thiadiazol-2-ylimino)indolin-2-one derivatives **5(a–j)**. The equimolar quantities of 5-substituted-1,3,4-thiadiazol-2-amine and isatin were sonicated in the presence of activated molecular sieves 3 Å at a temperature of 50 °C and at a frequency 20 kHz, and higher yields (73–92 %) and faster reaction times (43–75 min) were obtained when ultrasonic irradiation was used in comparison with conventional methods. The synthesized compounds were evaluated for anticonvulsant (MES and sc-PTZ model) and behavioral activity (actophotometer) in mice. The compounds **5b**, **5i** and **5j** have shown protection against MES model at 0.5- and 4-h period at dose level of 100 mg/kg, while the compound **5c** showed protection against sc-PTZ model at the same dose level. To exploit the mode of action of the synthesized compounds, docking study against sodium channel receptor was performed and the results revealed good binding interactions with the receptor. ADME properties of synthesized compounds were also analyzed and showed potential to develop as good oral drug candidates.

**Keywords** Molecular sieves · Ultrasound-mediated synthesis · Isatin–thiadiazole · Anticonvulsant activity · Docking study

## Introduction

Epilepsy is ubiquitous neurological disorder characterized by recurrent attack of seizures due to continuous firing threshold of neurons from cerebral origin, manifested as brief episodes of loss of consciousness (McNamara, 1999; Fisher *et al*., 2005). The epidemiological survey reveals that more than 50 million population around the globe suffer from epilepsy (Media Center, Epilepsy Fact Sheet; WHO, 2014). Currently available first-generation anticonvulsant agents like phenytoin, ethosuximide, benzodiazepines exhibit an unwanted side effect profile and failure to adequately control seizures (Bazil and Pedly, 1998; McCabe, 2000). These findings demand for the development of more effective and reliable anticonvulsant drugs (Kramer, 2001).

Ultrasound irradiation, in recent times, has achieved an important place in synthetic organic chemistry as a very effective and eco-friendly method for synthetic reactions (Mason, 1997). Ultrasound-promoted synthesis has gained popularity as they provide potentialities like small time cycles, cheaper reagents, increase in reaction rate and less extreme physical conditions (Mason, 1997; Suslick, 1990; Cella and Stefani, 2009). It can also be considered as important tool for conservation of energy and minimization of waste as compared to the convectional techniques (Saleh and Abd El-Rahman, 2009).

The microporous molecular sieves 3 Å are aluminosilicate minerals and have chemical formula $2/3K_2O{\cdot}1/3Na_2O{\cdot}Al_2O_3{\cdot}2SiO_2{\cdot}9/2H_2O$. Since 1990s, these molecular

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sieves have attracted considerable attention owing to their potential use in catalysis. Avelino Corma reviewed the synthesis of microporous to mesoporous molecular sieve materials and their use in catalysis for various synthetic methodologies (Corma, 1997). Molecular sieves find their application in catalytic reactions for the synthesis of ketimines and enamines (Westheimer and Taguchi, 1971).

In the past few years, several compounds containing isatin molecule make up a broad class due to its wide range of pharmacological activities (Pakravan *et al*., 2013). The anticonvulsant potential of isatin-containing compounds has been demonstrated by various research groups (Sridhar *et al*., 2002; Popp, 1984; Eggadi *et al*., 2013; Verma *et al*., 2004; Pandeya *et al*., 2001; Bhattacharya and Chakrabarti, 1998; Pandeya *et al*., 2002; Karali and Gursoy, 1994).

As shown in Fig. 1, the structure of acetazolamide contains thiadiazole moiety, which is carbonic anhydrase inhibitor that has been approved by US Food and Drug Administration (FDA) for treatment of seizures since 1953 (Foldvary-Schaefer and Falcone, 2003). Literature survey also reveals that thiadiazole nucleus is an important heterocyclic scaffold for the development of potential anticonvulsant agents (Chapleo *et al*., 1988; Stillings *et al*., 1986; Chapleo *et al*., 1986; Sharma *et al*., 2011). Based on the above facts of the literature, isatin–thiadiazole coupled moieties can be represented as privileged molecular scaffolds for anticonvulsant activity. So, these coupled heterocycles can be effectively used in the treatment of seizures, due to the synergistic effect of these two combined moieties.

In continuation of our studies on the synthesis of hybrid heterocycles as anticonvulsant agents by using improved green methodologies (Nikalje *et al*., 2011, 2012, 2014), we report a new, rapid, high-yielding and ultrasound-assisted synthesis of isatin–thiadiazole coupled derivatives along with their anticonvulsant activities. The synthesized compounds were designed on the basis of hypothesis of Unverferth *et al*., (1998) which suggested a common pharmacophoric pattern that is necessary for anticonvulsant activity, and the synthesized compounds follow a pharmacophoric pattern required for activity as shown in Fig. 2. The docking study and analysis of pharmacokinetic properties were studied suggesting that the compounds can be exploited as good anticonvulsant agent.

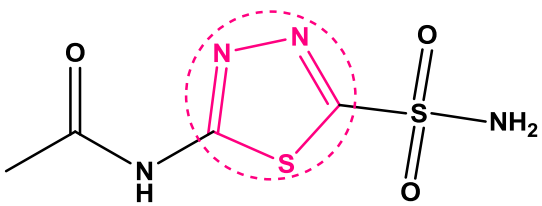



**Fig. 1** Acetazolamide

## Experimental

All the starting materials and reagents were purchased from Sigma-Aldrich, Merck and Qualigens and used without further purification. All the solvents were either of analytical grades or dried and distilled prior to use. Phosphorus oxychloride was used by distilling under reduced pressure. All the reactions were performed in oven-dried glasswares. The ultrasound sonicator (Sonics Vibra-cell, Model no. VCX 500) equipped with solid synthetic probe, 13 mm in tip diameter, operating at 20 kHz with a maximum power output of 500 W, was used for the synthesis of final title compounds. Thin-layer chromatography was performed on silica gel G pre-coated plates (Merck), and visualization of the developed chromatogram was performed by staining with iodine.

The NMR spectra of final titled compounds were recorded on Bruker Advance II (400 MHz), and infrared (IR) spectra were recorded for the compounds on JASCO FTIR (PS 4000) using KBr pallet. Elemental analysis (C, H and N) was done with a Shimadzu's FLASHEA112 analyzer, and all analyses were consistent with theoretical values (within ±0.5 %) unless indicated. The mass spectra were recorded on a waters Micromass ZQ 2000 spectrometer.

### General procedure for synthesis of 5-substituted 1,3,4-thiadiazol-2-amine 3(a–j)

5-Substituted-1,3,4-thiadiazol-2-amine derivatives were synthesized by refluxing equimolar quantities of thiosemicarbazide and substituted aromatic acids in phosphorus oxychloride, as per reported procedure (Mullick *et al*., 2011).

### Synthesis of 3-(5-substituted-1,3,4-thiadiazol-2-ylimino)indolin-2-one 5(a–j)

*Conventional method*

A mixture of substituted thiadiazole derivatives **3(a–j)** (1.0 mmol) and isatin **4** (1.0 mmol), in absolute ethanol, was heated under reflux for 6–8 h in the presence of glacial acetic acid (2.0 mmol) as a catalyst. Then, the reaction mixture was poured in ice-cold water and filtered under suction; the precipitate thus obtained was washed with water and recrystallized from ethanol.

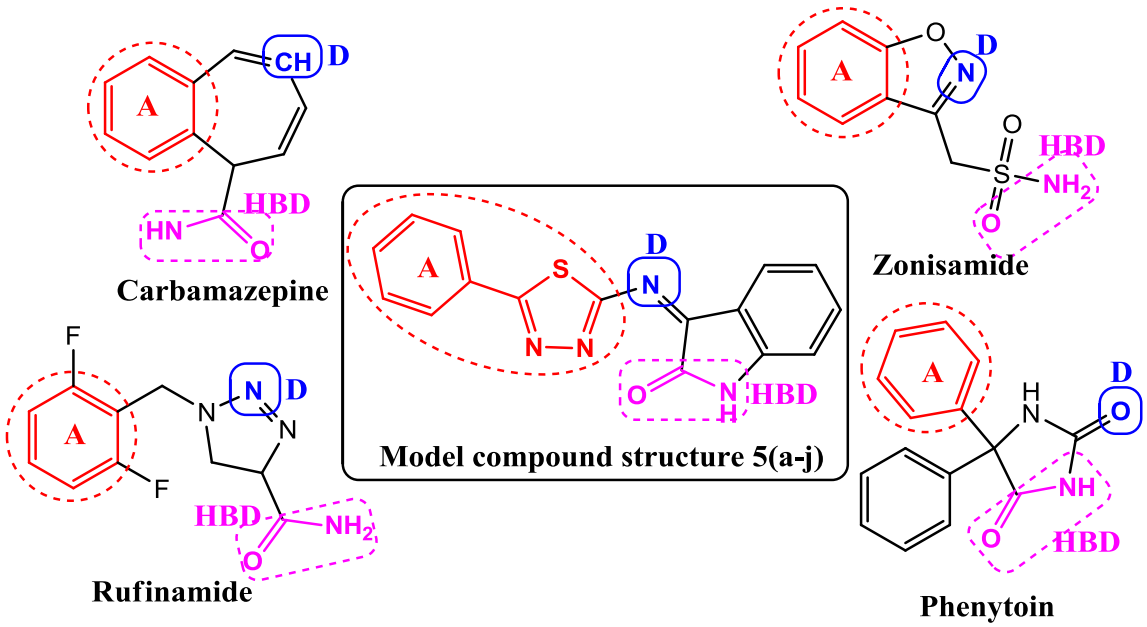



**Fig. 2** Pharmacophoric pattern of well-known anticonvulsants and model compound structure with essential elements

*Sonicated procedure*

A mixture of substituted thiadiazole derivatives **3(a–j)** (1.0 mmol) and isatin **4** (1.0 mmol), in absolute ethanol, was sonicated in absolute ethanol in the presence of activated molecular sieves 3 Å (1.0 g) at a temperature of 50 °C and frequency 20 kHz for a specified time given in Table 1. Then, the reaction mixture was poured in ice-cold water and filtered under suction; the precipitate thus obtained was washed with water and recrystallized from ethanol.

*3-(5-Phenyl-1,3,4-thiadiazol-2-ylimino)indolin-2-one* ***(5a)*** Yellowish crystals (EtOH); M.P. = 178–180 °C; IR (KBr, $\nu_{max}$, $cm^{-1}$); 3252 (NH of isatin), 3041 (C–H of Ar), 1731 (C=O),1675 (C=N), 1123 (C–S); $^{1}H$ NMR ($CDCl_3$, 400 MHz): δ = 7.39–8.01 (m, 9H, Ar ring), 8.26 (s, 1H, NH of indole); $^{13}C$ NMR ($CDCl_3$, ppm): δ = 117.5 (C, C-4), 120.5 (CH, C-8), 125.8 (CH, C-6), 128.4 (CH, C-19), 131.2 (CH, C-18), 141.4 (C, C-9), 150.7 (C, C-2), 163.8 (C, C-3), 175.4 (C, C-16); MS: m/z 307.8 (M + 1), Anal. Calcd. For $C_{16}H_{10}N_4OS$: C, 62.73; H, 3.29; N, 18.29; Found: C, 62.75; H, 3.30; N, 18.31.

*3-(5-(4-Chlorophenyl)-1,3,4-thiadiazol-2-ylimino)indolin-2-one* ***(5b)*** Dark-yellowish crystals (EtOH); M.P. = 152–154 °C; IR (KBr, $\nu_{max}$, $cm^{-1}$); 3263 (NH), 3033 (C–H of Ar), 1725 (C=O), 1666 (C=N), 1141 (C–S), 723 (C–Cl),

**Table 1** Comparison of reaction kinetics of conventional and ultrasonic irradiation methods for synthesis of compounds **5(a–j)**

| Entry | Conventional | | Ultrasonic irradiation | |
|---|---|---|---|---|
| | Time (h) | Yield (%) | Time (min) | Yield (%) |
| **5a** | 5 | 68 | 45 | 86 |
| **5b** | 6 | 63 | 50 | 92 |
| **5c** | 5 | 62 | 43 | 78 |
| **5d** | 7 | 58 | 55 | 82 |
| **5e** | 8 | 45 | 60 | 73 |
| **5f** | 8 | 56 | 65 | 80 |
| **5g** | 9 | 57 | 70 | 77 |
| **5h** | 7 | 61 | 55 | 81 |
| **5i** | 8 | 53 | 75 | 76 |
| **5j** | 7 | 63 | 60 | 83 |

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 7.24–8.09 (m, 8H, Ar ring), 8.14 (s, 1H, NH of indole); $^{13}$C NMR ($CDCl_3$, ppm): δ = 116.6 (C, C-4), 119.4 (CH, C-8), 125.8 (CH, C-6), 128.6 (CH, C-19), 135.8 (C, C-20), 141.5 (C, C-9), 150.5 (C, C-2), 165.8 (C, C-3), 176.8(C, C-16); MS: m/z 341.5 (M + 1), Anal. Calcd. For $C_{16}H_9ClN_4OS$: C, 56.39; H, 2.66; N, 16.44; Found: C, 56.36; H, 2.68; N, 16.46.

*3-(5-(2-Chlorophenyl)-1,3,4-thiadiazol-2-ylimino)indolin-2-one* ***(5c)*** Dark-yellowish crystals (EtOH); M.P. = 163–165 °C, IR (KBr, $\nu_{max}$, $cm^{-1}$); 3302 (NH), 3078 (C–H of Ar), 1743 (C=O), 1651 (C=N), 1173 (C–S), 746 (C–Cl), $^1$H NMR ($CDCl_3$, 400 MHz): δ = 7.42–8.14 (m, 8H, Ar ring), 8.16 (s, 1H, NH of indole); $^{13}$C NMR ($CDCl_3$, ppm): δ = 117.8 (C, C-4), 120.4 (CH, C-8), 124.8 (CH, C-6), 127.8 (CH, C-21), 128.9 (CH, C-22), 131.2 (CH, C-7), 132.8 (C, C-18), 136.8 (C, C-17), 141.2 (C, C-9), 150.5 (C, C-2), 163.5 (C, C-3), 174.5 (C, C-16); MS: m/z 341.8 (M + 1); Anal. Calcd. For $C_{16}H_9ClN_4OS$: C, 56.39; H, 2.66; N, 16.44; Found: C, 56.37; H, 2.65; N, 16.47.

*3-(5-p-Tolyl-1,3,4-thiadiazol-2-ylimino)indolin-2-one* ***(5d)*** Dark-gray crystals (EtOH), M.P. = 231–232 °C, IR (KBr, $\nu_{max}$, $cm^{-1}$); 3312 (NH), 3022 (C–H of Ar), 1730 (C=O), 1659 (C=N), 1173 (C–S), 1145 (C–S), $^1$H NMR ($CDCl_3$, 400 MHz): δ = 2.35 (s, 3H, $CH_3$ attached to phenyl), 7.25–8.45 (m, 8H, Ar ring), 8.21 (s, 1H, NH of indole); $^{13}$C NMR ($CDCl_3$, ppm): δ = 21.8 ($CH_3$, C-23), 117.5 (C, C-4), 120.8 (CH, C-8), 124.8 (CH, C-6), 127.5 (CH, C-21), 129.8 (CH, C-22), 132.7 (CH, C-20), 141.5 (C, C-9), 150.7 (C, C-2), 163.5 (C, C-3), 175.8 (C, C-16); MS: m/z 321.4 (M + 1), Anal. Calcd. For $C_{17}H_{12}N_4OS$: C, 63.73; H, 3.78; N, 17.49; Found: C, 63.75; H, 3.80; N, 17.52.

*3-(5-(4-Hydroxyphenyl)-1,3,4-thiadiazol-2-ylimino)indolin-2-one* ***(5e)*** Gray crystals (EtOH), M.P. = 129–131 °C, IR (KBr, $\nu_{max}$, $cm^{-1}$); 3572 (OH), 3325 (NH), 3075 (C–H of Ar), 1753 (C=O), 1643 (C=N), 1123 (C–S), $^1$H NMR ($CDCl_3$, 400 MHz): δ = 4.23 (s, 1H, OH attached to phenyl), 7.42–8.56 (m, 8H, Ar ring), 8.41 (s, 1H, NH of indole); $^{13}$C NMR ($CDCl_3$, ppm): δ = 117.5 (C, C-4), 119.7 (CH, C-8), 125.8 (CH, C-6), 128.5 (CH, C-21), 132.6 (CH, C-7), 141.8 (C, C-9), 150.8 (C, C-2), 158.8 (C, C-20), 163.8 (C, C-20), 174.8 (C, C-16); MS: m/z 323.3 (M + 1), Anal. Calcd. For $C_{16}H_{10}N_4O_2S$: C, 59.62; H, 3.13; N, 17.38; Found: C, 59.63; H, 3.15; N, 17.35.

*3-(5-(4-Nitrophenyl)-1,3,4-thiadiazol-2-ylimino)indolin-2-one* ***(5f)*** Greenish-yellow crystals (EtOH), M.P. = 190–192 °C, IR (KBr, $\nu_{max}$, $cm^{-1}$); 3256 (NH), 3039 (C–H of Ar), 1737 (C=O), 1619 (C=N), 1512 ($NO_2$), 1174 (C–S), $^1$H NMR ($CDCl_3$, 400 MHz): δ = 7.12–8.36 (m, 8H, Ar ring), 8.23 (s, 1H, NH of indole); $^{13}$C NMR ($CDCl_3$, ppm): δ = 118.4 (C, C-4), 119.7 (CH, C-8), 125.4 (CH, C-19), 129.7 (CH, C-5), 139.5 (CH, C-17), 149.5 (C, C-20), 151.1 (C, C-2), 163.5 (C, C-3), 175.2 (C, C-16); MS: m/z 352.5 (M + 1), Anal. Calcd. For $C_{16}H_9N_5O_3S$: C, 54.70; H, 2.58; N, 19.93; Found: C, 54.74; H, 2.60; N, 19.91.

*3-(5-(3,5-Dinitrophenyl)-1,3,4-thiadiazol-2-ylimino)indolin-2-one* ***(5 g)*** Greenish-yellow crystals (EtOH), M.P. = 128–130 °C, IR (KBr, $\nu_{max}$, $cm^{-1}$); 3321 (NH), 3045 (C–H of Ar), 1721 (C=O), 1657 (C=N), 1525 ($NO_2$), 1171 (C–S), $^1$H NMR ($CDCl_3$, 400 MHz): δ = 7.09–8.54 (m, 7H, Ar ring), 8.03 (s, 1H, NH of indole); $^{13}$C NMR ($CDCl_3$, ppm): δ = 117.5 (C, C-4), 120.8 (CH, C-8), 125.7 (CH, C-6), 129.7 (CH, C-18), 131.3 (CH, C-5), 136.8 (CH, C-17), 141.6 (C, C-9), 149.3 (C, C-19), 151.2 (C, C-2), 164.6 (C, C-4), 174.5 (C, C-16); MS: m/z 397.3 (M + 1), Anal. Calcd. For $C_{16}H_8N_6O_5S$: C, 48.49; H, 2.03; N, 21.20; Found: C, 48.51; H, 2.05; N, 21.22.

*3-(5-(2-Hydroxyphenyl)-1,3,4-thiadiazol-2-ylimino)indolin-2-one* ***(5 h)*** Gray crystals (EtOH), M.P. = 214–216 °C, IR (KBr, $\nu_{max}$, $cm^{-1}$); 3554 (OH), 3315 (NH), 3035 (C–H of Ar), 1735 (C=O), 1623 (C=N), 1142 (C–S), $^1$H NMR ($CDCl_3$, 400 MHz): δ = 5.45 (s, 1H, OH attached to phenyl), 7.42–8.16 (m, 8H, Ar ring), 8.14 (s, 1H, NH of indole), $^{13}$C NMR ($CDCl_3$, ppm): δ = 118.7 (C, C-4), 120.5 (CH, C-8), 121.5 (CH, C-21), 123.5 (C, C-17), 128.1 (CH, C-22), 131.6 (CH, C-20), 141.2 (C, C-9), 151.7 (C, C-2), 156.5 (C, C-18), 163.0 (C, C-3), 175.2 (C, C-16); MS: m/z 323.5 (M + 1), Anal. Calcd. For $C_{16}H_{10}N_4O_2S$: C, 59.62; H, 3.13; N, 17.38; Found: C, 59.65; H, 3.15; N, 17.40.

*2-(5-(2-Oxoindolin-3-ylideneamino)-1,3,4-thiadiazol-2-yl) phenyl acetate* ***(5i)*** Gray crystals (EtOH), M.P. = 149–151 °C, IR (KBr, $\nu_{max}$, $cm^{-1}$); 3236 (NH), 3039 (C–H of Ar), 1718 (C=O), 1747 (C=O of ester), 1685 (C=N), 1182 (C–S), $^1$H NMR ($CDCl_3$, 400 MHz): δ = 2.47 (s, 3H, $CH_3$ of acetate), 7.14–8.47 (m, 8H, Ar ring), 8.51 (s, 1H, NH of indole); $^{13}$C NMR ($CDCl_3$, ppm): δ = 22.7 ($CH_3$, C-3), 118.7 (C, C-20), 119.5 (C, C-24), 125.8 (CH, C-22), 126.6 (CH, C-8), 127.3 (CH, C-7), 129.1 (CH, C-6), 142.7 (C, C-18), 151.3 (C, C-18), 163.5 (C, C-19), 169.5 (C, C-1), 176.8 (C, C-12); MS: m/z 365.1 (M + 1), Anal. Calcd. For $C_{18}H_{12}N_4O_3S$: C, 59.33; H, 3.32; N, 15.38; Found: C, 59.35; H, 3.31; N, 15.40.

*3-(5-Styryl-1,3,4-thiadiazol-2-ylimino)indolin-2-one* ***(5j)*** Yellowish crystals (EtOH), M.P. = 200–202 °C, IR (KBr, $\nu_{max}$, $cm^{-1}$); 3236 (NH), 3039 (C–H of Ar), 1732 (C=O), 1653 (C=C of styryl), 1685 (C=N), 1182 (C–S), $^1$H NMR ($CDCl_3$, 400 MHz): δ = 6.95 (d, 1H, =CH-phenyl), 6.99 (d, 1H, =CH-thiadiazole), 7.24–8.19 (m, 9H, Ar ring), 8.21 (s, 1H, NH of indole); $^{13}$C NMR ($CDCl_3$, ppm): δ = 116.2 (CH, C-17), 117.9 (C, C-4), 119.2 (CH, C-8), 124.5 (CH,

C-6), 128.7 (CH, C-21), 128.3 (CH, C-5), 130.3 (CH, C-7), 134.3 (CH, C-18), 138.0 (C, C-19), 142.3 (C, C-19), 151.3 (C, C-2), 159.2 (C, C-9), 164.3 (C, C-3); MS: m/z 333.4 (M + 1), Anal. Calcd. For $C_{18}H_{12}N_4OS$: C, 65.04; H, 3.64; N, 16.86; Found: C, 65.06; H, 3.66; N, 16.89.

## Pharmacological method

A novel series of 3-(5-substituted-1,3,4-thiadiazol-2-ylimino) indolin-2-one was evaluated for anticonvulsant activity according to anticonvulsant drug development (ADD) program protocol (Krall *et al*., 1978; Porter *et al*., 1984). Male Swiss albino mice (CF-1 strain, 20–30 g) were used as experimental animals. Animals were divided into twelve groups, and each group of five animals was housed and allowed free access to water and food. A 12-h: 12-h light/dark cycle was maintained throughout the experimental studies. All the tested compounds were administered in suspension made up to 0.5 % Tween 80 in 0.9 % sodium chloride solutions and are used for MES and sc-PTZ study. Pentylenetetrazole (80 mg/kg) dissolved in 0.9 % sodium chloride solution was administered in the posterior midline of the mice, and the onset and severity of convulsions were noted for control group. The test group was administered with the selected compounds 0.5 h prior to the administration of PTZ. The statistical analyses were performed by one-way ANOVA followed by Student's *t* test to evaluate the results using GraphPad Prism software. All the values were expressed as mean ± SEM. The approval of the Institutional Animal Ethics Committee (CPCSEA/IAEC/Pharm. Chem.-20/2012-2013/78) of Y.B. Chavan College of Pharmacy, Aurangabad (Maharashtra, India), was taken prior to the start of the experiments.

### Anticonvulsant activity

The entire test compounds were administered *i.p.* injections in a volume of 0.01 ml/g for mice at doses of 100 mg/kg. Anticonvulsant activity was analyzed after 30 min and 4 h of drug administration. Then, MES and sc-PTZ model were studied for anticonvulsants evaluations using reported procedures.

#### *Neurotoxicity screening*

Rotarod test has been performed to detect the minimal motor deficit in mice. Animals were divided into groups of 5 and trained to stay on an accelerating rotarod that rotates at 10 rpm. The rod diameter was 3.2 cm. Trained animals (able to stay on the rotarod for at least two consecutive trials of 90 s each) were given an *i.p.* injection of the test compounds at dose of 100 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 the animal fell off the rod was determined.

### Behavioral activity

The behavioral activity of synthesized compounds was measured by actophotometer with the *i.p.* administration of drug (100 mg/kg) to mice. The mice were dropped in a box, and after 10 min, the behavior of animal was observed. Then, tested compounds were given to the animals, and after 0.5 and 4 h, animals were rested. The activity score was noted, and based on these results, % decrease in locomotor activity was calculated.

## Computational parameter

### The docking study

The docking study of synthesized compounds and the standard drug phenytoin was performed against crystal structure of sodium channel receptor (PDB ID: 1BYY) which is obtained from the Protein Data Bank (Rohl *et al*., 1999). The VLife MDS 4.3 package was used for docking study of titled compounds. The standard operating procedure implemented in VLife MDS 4.3 package was followed for GRIP batch docking of final synthesized compounds against three-dimensional structures of sodium channel receptors (VLife MDS 4.3, 2013).

### Distance mapping

In the distance mapping study, the distance between various groups of titled compounds and standard drugs was calculated on 3D optimized structures by ACD/3D viewer 8.04 version program. In conformational analysis of the clinically effective anticonvulsant drugs such as phenytoin and lamotrigine, a molecular model was suggested on the basis of molecular dynamics distance estimations (Wong *et al*., 1986).

### Determination of ADME properties

The synthesized compounds were determined for prediction of ADME properties. The various ADME properties studied including polar surface area (TPSA), number of rotatable bonds, molecular volume, number of hydrogen donors, number of hydrogen acceptors and violations of Lipinski rule were calculated by Molinspiration online property toolkit. %ABS was calculated by using formula:

%ABS = 109 − (0.345 × TPSA) (Molinspiration Cheminformatics, 2014).

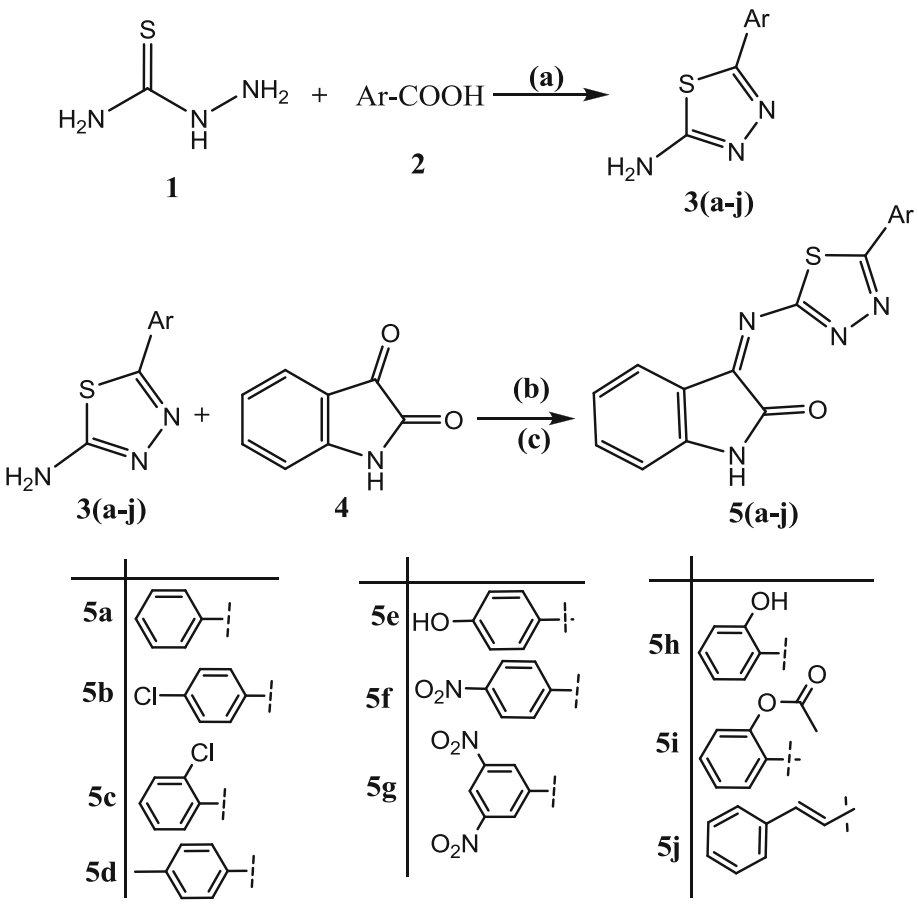
## Results and discussion

### Chemistry

The synthetic protocol for synthesis of titled compounds 3-(5-substituted-1,3,4-thiadiazol-2-ylimino)indolin-2-one **5(a–j)** is outlined in Scheme 1. The compounds 5-substituted 1,3,4-thiadiazol-2-amine **3** were synthesized by refluxing equimolar quantities of thiosemicarbazide **1** and substituted carboxylic acids **2** in $POCl_3$ as per reported procedure (Mullick *et al*., 2011).

Further synthesis of 3-(5-substituted-1,3,4-thiadiazol-2-ylimino) indolin-2-one **5(a–j)** was achieved by using both conventional and ultrasound irradiation methods. The conventional synthesis of titled compounds **5(a–j)** was performed by refluxing 5-substituted 1,3,4-thiadiazol-2-amine **3** with isatin **4** using glacial acetic acid in absolute ethanol for the time as indicated in Table 1. The conventional method has taken more time, i.e., 5–9 h, and resulted in low yields (45–68 %). In order to increase the yields and lower the reaction time, we performed same set of reactions by ultrasound irradiation using activated molecular sieves 3 Å. In ultrasound-mediated synthesis of titled compounds, the equimolar quantities of 5-substituted 1,3,4-thiadiazol-2-amine **3** and isatin **4** were sonicated in the presence of activated molecular sieves 3 Å at a temperature of 50 °C and frequency 20 kHz at indicated time given in Table 1. From Table 1, it was concluded that higher yields (73–92 %) and faster reaction time (43–75 min) were obtained when ultrasonic irradiation was used in comparison with conventional methods.

The ultrasound-assisted synthesis technique works on the principle of cavitation. As ultrasound passes through liquid, the liquid can produce bubbles. These bubbles can undergo a violent collapse, which generates very high pressures and temperatures, inducing molecular fragmentation, and highly reactive species are locally produced. In addition, ultrasound is known to generate extremely fine emulsions from mixtures of immiscible liquids to enhance mass transfer from one phase into the other. One of the main consequences of these emulsions is the dramatic increase in the interfacial contact area between the reactants and an increase in the region over which any reaction between species dissolved in the different liquids can take




**Scheme 1** Synthetic protocol for titled compounds **5(a–j)**. Reagents and conditions: (*a*) $POCl_3$, reflux; (*b*) convectional: EtOH, AcOH, reflux; (*c*) ultrasound irradiation: EtOH, molecular sieves 3 Å

place (Cella and Stefani, 2009). All of these parameters can cause the reaction to take place rapidly.

### Reusability of molecular sieves

We also investigated reusability and recycling of molecular sieves. After completion of reaction mixture, molecular sieves could be recovered by simple filtration, washed with methanol and dried. Thus, recovery of molecular sieves involves a simple filtration and avoids a tedious workup procedure. Then, these recovered molecular sieves were reused for further reactions. The recycled molecular sieves showed no appreciable loss in activity even after the third cycle. Listed below are the cycle number and yield of **5b** (%):1, 92; 2, 91; 3, 89, as shown in Fig. 3.

### Anticonvulsant activity

The anticonvulsant screening was performed using male Swiss albino mice (CF-1 strain, 20–30 g). The anticonvulsant activity of synthesized compounds was assessed by two models, namely maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (sc-PTZ). Neurotoxicity and behavioral study was analyzed by rotarod and actophotometer, respectively. All the synthesized compounds screened for anticonvulsant activity showed protection against MES test. In the MES testing of all synthesized compounds (Table 2), the compounds **5b, 5c, 5e, 5f, 5i** and **5j** showed protection at the time interval 0.5 h and **5a, 5b, 5d, 5 g, 5i** and **5j** showed protection at the dose 100 mg/kg in time interval 4 h. The compounds **5b, 5i** and **5j** showed protection at both time intervals at the same dose. Several compounds of these series were also found to be active in sc-PTZ test (Table 2). The compound **5c** showed protection at both time intervals. The compounds **5b, 5c, 5e, 5 g** and **5j** showed protection at 0.5 h, and compounds **5c, 5d, 5f, 5 h** and **5i** showed protection at 4 h. In this study, the compounds **5b, 5e, 5i** and **5j** did not show neurotoxicity in the maximum dose of 100 mg/kg (Table 2). From the behavioral activity of synthesized compounds as shown in Table 3 using actophotometer, the compounds **5a, 5b, 5c, 5e, 5 g** and **5j** showed no behavioral despair effect when compared to diazepam at 0.5 h. The compounds **5b, 5c, 5e, 5 g, 5 h** and **5i** showed no behavioral despair effect when compared to diazepam at 4 h. Compounds **5d** and **5f** were found to decrease behavioral activity of the animals when compared to diazepam (Table 3).

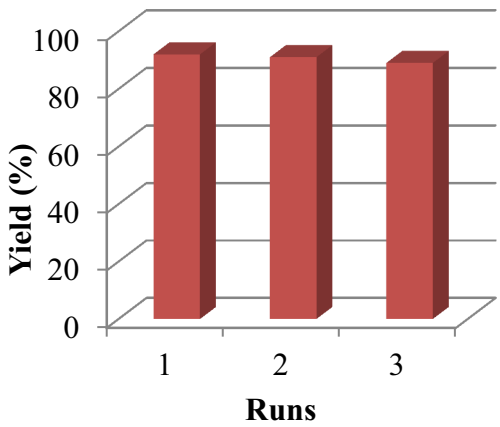



**Fig. 3** Recycling study of molecular sieves

### SAR analysis for synthesized compounds

The structure–activity relationship reveals some important facts about the structure-specific variation in anticonvulsant activity. The significant anticonvulsant activity of tested compounds depended on the presence of the combination of Schiff's bases of isatin and thiadiazole ring in one molecule; thus, the Schiff's bases of isatin and thiadiazole were more active in comparison with Schiff's bases of isatin. The nature of a substituent in the aryl fragment attached to thiadiazole ring also had an influence on the anticonvulsant activity. Therefore, the introduction of an electron-withdrawing group, chloro substituent showed promising anticonvulsant activity in comparison with electron-donor groups –OH, $–CH_3$ and $-OCH_3$. The substitution of 4-chloro (**5b**) on phenyl ring attached to thiadiazole ring had shown protection against MES model, and 3-chloro (**5c**) substituent had shown protection against sc-PTZ model. Hence, it can be proved that ortho- and para-chloro substitution makes a large difference in MES and sc-PTZ model. The substitution of $3\text{-}OCOCH_3$ of phenyl ring (**5i**) gives a significant anticonvulsant activity. Alkene linkage between thiadiazole and phenyl ring (**5j**) can also be considered for a significant anticonvulsant activity (Fig. 4).

### Computational parameters

*The docking study*

The synthesized compounds **5(a–j)** and standard drug phenytoin were docked against sodium channel receptor (PDB ID: 1BYY) to understand the binding interactions, docking calculation and hydrogen bond interactions by VLife MDS 4.3 package and are shown in Table 4. The interaction energy of the compounds **5(a–j)** and their anticonvulsant activity showed the corresponding results. The isatin and thiadiazole rings of these compounds **5(a–j)** held in the active pocket by forming various van der

**Table 2** Anticonvulsant and neurotoxicity screening of compounds

| Entry | MES screen | | sc-PTZ screen | | Neurotoxicity screen |
|---|---|---|---|---|---|
| | 0.5 h | 4 h | 0.5 h | 4 h | 4 h |
| **5a** | – | 100 | – | – | X |
| **5b** | 100 | 100 | 100 | – | – |
| **5c** | 100 | – | 100 | 100 | X |
| **5d** | – | 100 | | 100 | 100 |
| **5e** | 100 | – | 100 | – | – |
| **5f** | 100 | – | – | 100 | 100 |
| **5g** | – | 100 | 100 | – | X |
| **5h** | – | 100 | – | 100 | 100 |
| **5i** | 100 | 100 | – | 100 | – |
| **5j** | 100 | 100 | 100 | – | – |
| Phenytoin | 100 | 100 | X | X | X |
| Sodium valproate | X | X | 100 | – | X |

Dose 100 mg/kg of the compound was 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. (X) denotes not tested

**Table 3** Behavioral study of compounds using actophotometer

| Entry | Activity score | Posttreatment[a] | |
|---|---|---|---|
| | Control (24 h before) | 0.5 h | 4 h |
| **5a** | 167.76 ± 5.757 | 126.62 ± 2.943 | 110.05 ± 4.930 ns |
| **5b** | 291.38 ± 3.829 | 157.02 ± 3.647 | 205.59 ± 5.278 |
| **5c** | 249.59 ± 3.970 | 132.18 ± 3.277 | 141.03 ± 3.808 |
| **5d** | 188.41 ± 3.894 | 70.58 ± 3.473 | 89.41 ± 2.839 |
| **5e** | 234.82 ± 4.821 | 152.60 ± 3.076 | 152.62 ± 3.076 |
| **5f** | 145.36 ± 5.046 | 73.39 ± 4.366 ns | 111.79 ± 3.484 ns |
| **5g** | 283.01 ± 4.037 | 111.78 ± 3.484 | 219.08 ± 4.658 |
| **5h** | 145.41 ± 5.163 | 57.23 ± 3.367 | 119.60 ± 4.771 ns |
| **5i** | 169.40 ± 4.697 | 66.62 ± 3.043 | 136.35 ± 6.831 |
| **5j** | 215.17 ± 5.122 ns | 124.17 ± 5.093 | 102.42 ± 6.038 ns |
| Diazepam[b] | 209.39 ± 3.600 | 87.200 ± 3.308 | 116.81 ± 3.470 |

[a] Each value represents the mean ± SEM significantly different from the control at $p < 0.05$, ns denotes not significant at $p < 0.05$ (Student's *t* test), locomotor activity score was measured for 10 min

[b] The compound was tested at dose level of 4 mg/kg (*i. p.*)

Waals interactions with the sodium channel receptor. The various van der Waals interactions occurred between these compounds and active site of receptor include MET1490, LYS1495, LYS1496, TYR1498, ASN1499, LYS1502, LEU1504 and SER1506. The active (MES model) compounds **5b**, **5i** and **5j** showed lowest binding energy that is −74.02, −72.68 and −72.67 kcal/mol, respectively. The -$CH_3$ substituent on phenyl ring of compounds **5d** and **5i** had formed hydrophobic interactions with amino acid residues MET1490 and LYS1495, and LYS1496, respectively. No other substituent of phenyl ring had shown any interactions with receptor. The various groups like O=C of isatin, nitrogen atoms of thiadiazole, C=N of Schiff's base and NH of isatin have shown hydrogen bond interactions with receptor. The amino acid residues like LYS1495, LEU1504, GLY1505 and SER1506 had taken part in hydrogen bonding. Phenytoin had shown good binding interaction energy that is −68.52 kcal/mol. Phenytoin had formed various hydrophobic and van der Waals interactions with amino

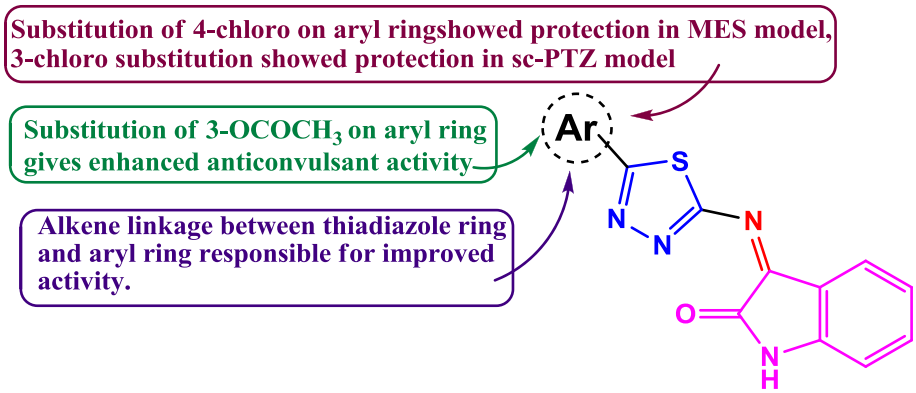



**Fig. 4** SAR analysis of synthesized compounds **5(a–j)**

**Table 4** Docking statistics of synthesized compounds against sodium channel receptor

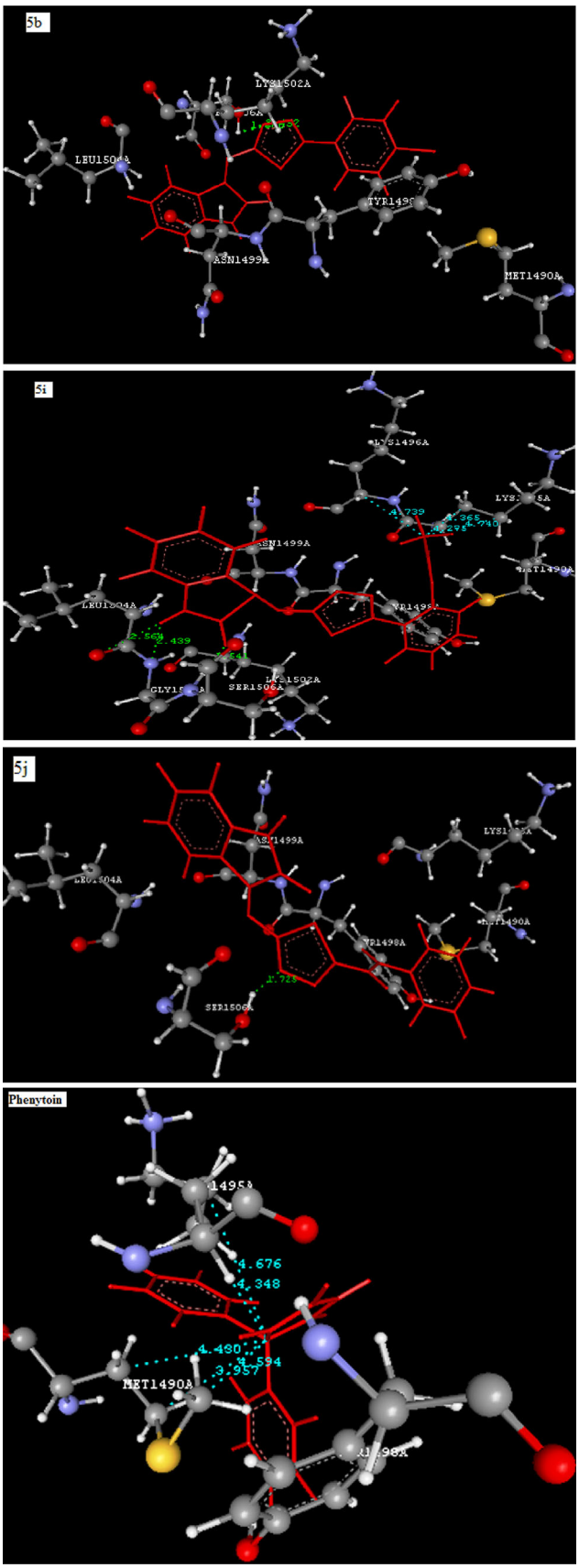
| Entry | Affinity (kcal/mol) | H-bonds | H-bonding ligand | | H-binding receptor | | | H-bonds length (Å) |
|---|---|---|---|---|---|---|---|---|
| | | | Element | Atom No. | Residue | Element | Atom No. | |
| **5a** | −64.18 | 01 | O | 22 | SER1506 | H | 342 | 2.565 |
| **5b** | −74.02 | 02 | N | 08 | SER1506 | H | 342 | 2.452 |
| | | | N | 09 | SER1506 | H | 342 | 1.600 |
| **5c** | −64.29 | 01 | O | 22 | SER1506 | H | 342 | 2.580 |
| **5d** | −64.07 | 01 | N | 09 | SER1506 | H | 342 | 2.372 |
| **5e** | −65.84 | 01 | H | 28 | LYS1495 | O | 138 | 1.978 |
| **5f** | −65.29 | 01 | N | 09 | SER1506 | H | 342 | 2.452 |
| **5g** | −55.04 | – | – | – | – | – | – | – |
| **5h** | −62.00 | 01 | N | 09 | SER1506 | H | 342 | 2.328 |
| **5i** | −72.68 | 03 | H | 31 | LEU1504 | O | 309 | 2.564 |
| | | | H | 31 | GLY1505 | N | 325 | 2.439 |
| | | | O | 22 | SER1506 | H | 338 | 1.541 |
| **5j** | −72.67 | 01 | N | 03 | SER1506 | H | 342 | 1.725 |
| Phenytoin | −68.52 | – | – | – | – | – | – | – |

acids residues like MET1490, LYS1495 and TYR1498 and had not shown any hydrogen-bonding interaction with sodium channel receptor.

The interactions of most active compounds **5b**, **5i**, **5j** and the standard drug phenytoin with sodium channel receptor are shown in Fig. 5. The amino acid SER1506 (2.452 Å) had formed hydrogen bonds with both nitrogen atoms of thiadiazole ring of compound **5b**. The compound **5i** had formed three hydrogen bonds that is LEU1504-HN of isatin (2.464 Å), GLY1505-HN of isatin (2.439 Å) and SER1506-O=C of isatin (1.541 Å). On the basis of activity data and docking result, it was observed that compounds **5b**, **5i** and **5j** have potential to inhibit sodium channel receptor and can be developed as lead for potent anticonvulsant agents.

*Distance mapping study*

In the distance mapping study, the distance between various groups of titled compounds and standard drugs was calculated. In this work, we selected well-known and structurally different compounds with different mechanism of action so as to propose a general pharmacophore model. It involves the correlation of well-known compounds with titled compounds. This correlation involves at least one aryl unit, electron-donor atoms and NH group in the spatial arrangement which is recommended for good pharmacological activity. The energy minimization of standard compounds and titled compounds was performed and analyzed. The average distance between each point was calculated and examines whether they satisfies the




◀**Fig. 5** Docking study of compounds **5b, 5i, 5j** and phenytoin with sodium channel receptor (PDB ID: 1BYY). Ligands are shown in *red color*. Hydrogen bonds are shown in *green color* (Color figure online)

condition for structural perquisites. It was found that the synthesized compounds fulfill the essential needs for the pharmacophores in comparison with average distance requirement as per data presented in Table 5.

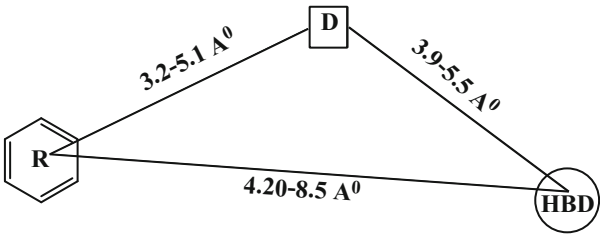
*Prediction of ADME properties*

We had analyzed various physical descriptors and pharmaceutically relevant properties for ADME prediction by using Molinspiration online property toolkit. The results are summarized in Table 6. All the compounds **5(a–j)** showed significant values for the various parameters analyzed and are within the range of accepted values. Among the synthesized compounds, none of the synthesized compounds had violated the Lipinski's rule of five. The value of % absorption (ABS) and polar surface area (TPSA) for synthesized compounds indicated good oral bioavailability of the compounds. The parameters, like number of rotatable bonds and number of rigid bonds are linked with intestinal absorption result, showed that all synthesized compounds **5(a–j)** had good absorption and making them potentially promising agents for treatment of seizures.

## Conclusion

A series of ten 3-(5-substituted-1,3,4-thiadiazol-2-ylimino)indolin-2-one derivatives **5(a–j)** were synthesized using conventional and ultrasound irradiation methods. Faster reaction time and high yields of the synthesized compounds were obtained in ultrasonic irradiation using molecular sieves 3 Å in comparison with the conventional method. The synthesized compounds were investigated for anticonvulsant and behavioral activities with the hope of discovering new structure leads serving as potential anticonvulsant agents. The compounds **5b**, **5i** and **5j** showed a significant activity in MES model, and compound **5c** showed protection in sc-PTZ model at the dose of 100 mg/kg at a time interval of 0.5 h and 4 h when compared with the standard drug. Most of the synthesized compounds exhibited lesser behavioral activity and neurotoxicity compared to clinically effective drugs. Further, molecular docking study strongly supports the assumption that these compounds may be involved in the inhibition of sodium channel receptor. Our analysis of the distance mapping relationship showed that the titled compounds fulfill the essential demand of pharmacophores when compared with other well-known anticonvulsants. Also, none of the synthesized compounds have violated Lipinski's rule of five, thus showing good drug-like properties.

**Table 5** Distance range between the essential structure elements R, D and HBD




| Compounds | R-HBD | R-D | D-HBD |
|---|---|---|---|
| Phenytoin | 3.58 | 3.77 | 2.21 |
| Lamotrigine | 6.44 | 4.87 | 4.06 |
| Lead compounds | 6.79 | 5.1 | 4.01 |

**Table 6** Pharmacokinetic parameter important for good oral bioavailability of compounds

| Entry | Milog P | %ABS | TPSA ($A^2$) | MW | n-ON acceptors | n-OHNH donors | Lipinski's violations | n-ROTB | MV |
|---|---|---|---|---|---|---|---|---|---|
| Rule | 1–5 | – | – | <500 | <10 | <5 | ≤1 | | |
| **5a** | 3.37 | 88.77 | 58.64 | 305.36 | 4 | 1 | 0 | 2 | 257.22 |
| **5b** | 4.05 | 88.77 | 58.64 | 339.80 | 4 | 1 | 0 | 2 | 270.15 |
| **5c** | 4.00 | 88.77 | 58.64 | 339.80 | 4 | 1 | 0 | 2 | 270.75 |
| **5d** | 3.82 | 88.77 | 58.64 | 319.39 | 4 | 1 | 0 | 2 | 273.78 |
| **5e** | 2.89 | 81.79 | 78.87 | 321.36 | 5 | 2 | 0 | 2 | 265.23 |
| **5f** | 3.33 | 72.96 | 104.47 | 350.35 | 7 | 1 | 0 | 3 | 280.55 |
| **5g** | 3.22 | 57.15 | 150.29 | 395.35 | 10 | 1 | 0 | 4 | 303.85 |
| **5h** | 3.10 | 81.79 | 78.87 | 321.36 | 5 | 2 | 0 | 2 | 265.25 |
| **5i** | 2.87 | 79.70 | 84.95 | 363.39 | 6 | 1 | 0 | 4 | 301.75 |
| **5j** | 3.56 | 88.77 | 58.64 | 331.40 | 4 | 1 | 0 | 3 | 284.63 |

% ABS—percentage of absorption, TPSA—topological polar surface area, n-ROTB—number of rotatable bonds, MW—molecular weight, MV—molecular volume, n-OHNH—number of hydrogen bond donors, n-ON—number of hydrogen bond acceptors

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