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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Synthesis of some urea and thiourea derivatives of naphtha[1,2-*d*]thiazol-2-amine as anti-Parkinsonian agents that cause neuroprotection against haloperidol-induced oxidative stress in mice

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**Abstract** A series of *N*-(substituted phenyl)-*N*′-(naphtha[1,2-*d*]thiazol-2-yl)urea and thiourea derivatives were synthesized starting from *N*-naphthylthiourea. The structures were confirmed by spectral and elemental analyses. The newly synthesized compounds were found to possess anti-Parkinsonian and antioxidant activities. Anti-Parkinsonian activity was evaluated on haloperidol-induced catalepsy in mice by employing the standard bar test. All of the synthesized compounds ameliorated the catalepsy induced by haloperidol in mice. The most potent compounds (**5**, **6**, **22**, and **29**) were selected for biochemical evaluation from the brain homogenate and were found to be effective in decreasing the elevated levels of malondialdehyde while restoring the cellular defense mechanisms such as glutathione content as well as glutathione peroxidase and superoxide dismutase activities in haloperidol-treated mice, suggesting the role of free radicals in the pathophysiology of haloperidol-induced catalepsy and possible antioxidant action of title compounds.

**Keywords** Parkinson's disease · Naphtha[1,2-*d*]thiazol-2-amine · Urea/thiourea derivatives · Neuroprotection

## Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, characterized by a specific loss of dopaminergic neurons in the substantia nigra pars compacta and affecting about 1% of the population above the age of 60 years (Abou-Sleiman *et al.*, 2006). The major clinical symptoms of PD include bradykinesia, postural instability, rigidity and tremor; furthermore, a number of

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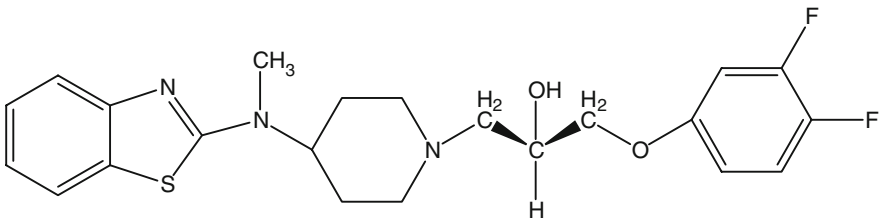
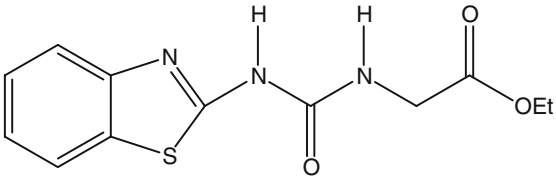
patients also suffer from anxiety, depression, autonomic disturbances, and dementia. The underlying cause of this selective cell death is not understood, although several hypotheses have been advanced (Olanow and Tatton, 1999). Among the many pathogenic mechanisms thought to contribute to the demise of dopamine neurons in PD, oxidative stress has received the most attention because endogenous dopamine undergoes both enzymatic and nonenzymatic oxidative metabolism resulting in the formation of reactive oxygen species (ROS) in the substantia nigra (Jenner, 2003). Post mortem studies in PD brains demonstrate increased iron, decreased glutathione (GSH; Sian *et al*., 1994), decreased activities of several antioxidant enzymes viz. glutathione peroxidase (GSH-Px; Kish *et al.*, 1985) and superoxide dismutase (SOD; Saggu *et al.*, 1989), increased levels of the lipid peroxidation (LPO) product malondialdehyde (MDA) and oxidative damage to lipids and proteins implicating oxidative stress in PD (Dexter *et al*., 1986; 1989; Przedborski and Ischiropoulos, 2005).

Pharmacological therapy of PD is presently aimed at symptomatic control because clinically effective neuroprotectants, capable of slowing the progression of nigral dopaminergic neuron degeneration, are yet to be identified. Symptomatic therapy is most effectively accomplished by replacing dopamine with levodopa; however, in a vast majority of PD patients, nonphysiological stimulation of dopamine receptors generates motor fluctuations (e.g., dyskinesias), which are responsible for a reduction of the clinical response over the years (Obeso *et al*., 2000). Based on the evidence for an oxidative component in PD, and in view of the complications associated with levodopa therapy, an alternative approach to the treatment of this disorder would be the use of neuroprotective or antioxidant therapy to prevent or slow down the degeneration of these neurons.

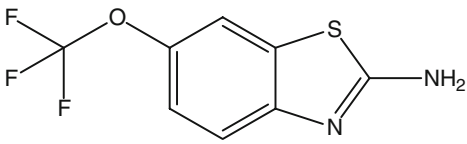
For many years, thiazole derivatives have been the subject of most structural and medicinal studies because of their biological potential. They are of interest as potential neuroprotective agents (Jeremiah *et al*., 2004; Azam *et al*., 2008a) as well as the possible core skeletons of adenosine receptor antagonists with moderate affinity and selectivity at the $A_{2A}$ receptor site (van Muijlwijk-Koezen *et al.*, 2001). Benzothiazoles are highly interesting molecules for drug development, because they are known to be useful for treating neurodegenerative disorders (Jimonet *et al*., 1994). Among the most efficient compounds, lubeluzole (Fig. 1) has been shown experimentally to preserve neurological function and reduce infarct volume in animal models of focal brain ischemia, (De Ryck *et al*., 1996; Aronowski *et al*., 1996) while other derivatives such as KHG21834 (Fig. 1) were capable of protecting PC12 cells and cortical and mesencephalic neurons from amyloid $\beta$-induced degeneration (Choi *et al*., 2007). In addition, riluzole (Fig. 1), a $Na^+$ channel blocker with antiglutamatergic activity, is effective against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurodegeneration of the nigrostriatal dopaminergic neuronal pathway and contains a benzothiazole ring (Araki *et al*., 2001). Moreover, riluzole prolongs survival and delays muscle strength deterioration in mice with progressive motor neuronopathy (Kennel *et al*., 2000) and shows neuroprotection in gerbil model of transient global ischemia (Bae *et al*., 2000). Also, some fused benzothiazoles (Brabander *et al*., 1999) and amino-benzothiazole derivatives (Mantegani *et al*., 2002) are reported to be useful for the therapeutic or



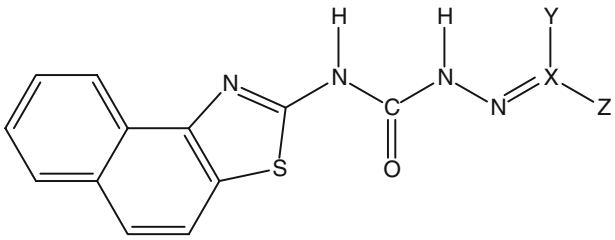

**I** : Lubeluzole




**II** : KHG21834




**III** : Riluzole




**IV** : Naphtha[1,2-*d*]thiazol-2-amine derivatives

**Fig. 1** Structure of some cited molecules

prophylactic treatment of humans suffering from ageing of, or degenerative diseases of the nervous system which are associated with oxidative stress.

The urea functionality is a key structural element of many biologically active compounds including neuroprotectants (Di Fabio *et al*., 1999; Choi *et al*., 2007). Furthermore, a series of urea substituted benzothiazoles are said to be effective in controlling or prevention of PD (Flohr *et al*., 2003, 2004). In our previous work, a series of naphtha[1,2-*d*]thiazol-2-amine derivatives (Fig. 1) were found to act by reducing the formation of MDA and increasing the formation of SOD and GSH-Px in mice brain, suggesting their neuroprotective properties (Azam *et al*., 2008a). In addition, the study of naphthalene derivatives has become of much interest in recent

years on account of their antioxidant (Foti *et al*., 2002; Lean-Teik *et al*., 2007) and anti-Parkinsonian (Backstrom *et al.*, 2005) activities. Their antagonistic role against l-glutamate-mediated excitotoxicity in the central nervous system has been documented (Baker *et al*., 2005).

Based on these observations and as part of our ongoing research program aiming at the synthesis of variety of heterocyclic systems for biological and pharmacological evaluation (Amir and Azam 2004a, b; Azam *et al*., 2007a, 2008a, b), I report here the synthesis of several urea and thiourea derivatives derived from naphtha[1,2-*d*]thiazol-2-amine to study their structure–activity relationship. The compounds were evaluated for haloperidol-induced catalepsy model of PD. The extent of oxidative stress has been evaluated by measuring MDA level, GSH content and antioxidant enzymes (SOD and GSH-Px) activities from brain homogenate in selected compounds. Part of this work has been presented in an abstract form (Azam *et al*., 2007b).

## Materials and methods

### Chemistry

Synthetic starting material, reagents, and solvents were of analytical reagent grade or of the highest quality commercially available and were purchased from Aldrich Chemical Co. and Merck Chemical Co. and were dried when necessary. The progress of the reactions was monitored by thin-layer chromatography (TLC) with $F_{254}$ silica-gel precoated sheets (Merck) using chloroform/ethylacetate (95:5) as eluent; ultraviolet (UV) light and iodine vapors were used for detection. Infrared (IR) spectra were recorded, as KBr pellets, on a Schimadzu 8201 PC Fourier-transform infrared (FT-IR) spectrophotometer and wavenumbers are given in $cm^{-1}$. The mass spectra were recorded on Jeol SX-102 fast atom bombardment (FAB). $^1H$ nuclear magnetic resonance (NMR) spectra, in dimethyl sulfoxide (DMSO)-$d_6$ solution, were recorded on a Bruker DRX-300 instrument at 298 K. Chemical shifts are reported as ppm relative to tetramethyl silane (TMS) as an internal standard. Melting points (°C) were determined with an open glass capillary tube and are reported uncorrected. Elemental analyses were performed on Elementar Vario EL III instrument. The found values for C, H, and N were always within 0.4% of the theoretical ones.

### Synthesis of the compounds

Naphtha[1,2-*d*]thiazol-2-amine (**2**) was synthesized according to our reported method (Azam *et al*., 2008a).

*General procedure for the synthesis of urea derivatives **3–19***

To a solution of **2** (0.4 g, 0.002 mol) in 25 ml dry acetonitrile, a 1.5 molar quantity of appropriate isocyanate in 5 ml dry acetonitrile was added dropwise at room

temperature. The mixture was stirred for 1–4 h until the completion of the reaction and the resultant precipitate was filtered, washed with acetonitrile, and dried. The product was recrystallized from 95% ethanol. The physical data of the compounds are presented in Table 1.

*General procedure for the synthesis of thiourea derivatives* ***20–32***

To a solution of **2** (0.4 g, 0.002 mol) in 25 ml dry acetonitrile, a 1.5 molar quantity of appropriate isothiocyanate in 5 ml dry acetonitrile was added dropwise at room temperature. The mixture was refluxed with stirring for 1–4 h until the completion of the reaction and the resultant precipitate obtained after cooling of the reaction mixture was filtered, washed with acetonitrile, and dried. The product was recrystallized from 95% ethanol. The physical data of the compounds are presented in Table 1.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-phenylurea (**3**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3236 (NH), 3061, 2965 (Ar–H), 1689 (C=O), 1605 (C=N), 1502 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 6.58–6.73–7.97 (m, 10H, Ar–H), 8.40 (d, 1H, $J = 9.42$ Hz), 9.32 (s, 1H, NH), 10.57 (br s, 1H, NH); MS (FAB) *m/z* 320 $(M + 1)^+$.

*1-(4-Methoxyphenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**4**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3200 (NH), 3064, 2952 (Ar–H), 1692 (C=O), 1619 (C=N), 1509 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.77 (s, 3H, $OCH_3$), 6.84 (d, 2H, $J = 8.79$ Hz), 7.41 (d, 2H, $J = 8.76$ Hz), 7.46–7.80 (m, 4H, Ar–H), 7.88 (d, 1H, $J = 7.89$ Hz), 8.50 (d, 1H, $J = 8.04$ Hz), 8.72 (br s, 1H, NH), 10.62 (s, 1H, NH); MS (FAB) *m/z* 350 $(M + 1)^+$.

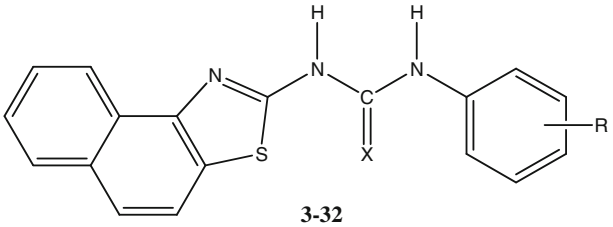
*1-(2-Methoxyphenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**5**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3200 (NH), 3120, 2945 (Ar–H), 1697 (C=O), 1608 (C=N), 1531, 1460 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.90 (s, 3H, $OCH_3$), 6.86-7.55 (m, 4H, Ar–H), 7.61 (d, 2H, $J = 8.64$ Hz), 7.74 (d, 1H, $J = 8.61$ Hz), 7.84 (d, 1H, $J = 7.92$ Hz), 8.21 (d, 1H, $J = 7.32$ Hz), 8.53 (d, 1H, $J = 7.77$ Hz), 9.89 (br s, 1H, NH), 11.15 (s, 1H, NH); MS (FAB) *m/z* 350 $(M + 1)^+$.

*1-(2,4-Dimethoxyphenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**6**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3192 (NH), 3096, 2959 (Ar–H), 1679 (C=O), 1608 (C=N), 1528 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.80 (s, 3H, 4-$OCH_3$), 3.94 (s, 3H, 2-$OCH_3$), 6.49–7.92 (m, 7H, Ar–H), 8.10 (d, 1H, $J = 8.73$ Hz), 8.60 (d, 1H, $J = 8.04$ Hz), 9.12 (s, 1H, NH), 10.96 (br s, 1H, NH); MS (FAB) *m/z* 380 $(M + 1)^+$.

**Table 1** Characterization data of the urea and thiourea derivatives **3–32**



**3-32**

| Compound | R | X | Yield (%) | M.P. (°C) | Mol. formula | Mol. weight | Nitrogen estimation (calculated/found) | R*f*[a] | log *P*[b] |
|---|---|---|---|---|---|---|---|---|---|
| **3** | H | O | 78 | 322 | $C_{18}H_{13}N_3OS$ | 319.38 | 13.16/13.09 | 0.38 | 4.65 |
| **4** | 4-$OCH_3$ | O | 86 | 260 | $C_{19}H_{15}N_3O_2S$ | 349.41 | 12.03/12.08 | 0.76 | 4.60 |
| **5** | 2-$OCH_3$ | O | 96 | 242 | $C_{19}H_{15}N_3O_2S$ | 349.41 | 12.03/12.07 | 0.79 | 4.60 |
| **6** | 2,4-$OCH_3$ | O | 55 | 228 | $C_{20}H_{17}N_3O_3S$ | 379.43 | 11.07/11.11 | 0.55 | 4.37 |
| **7** | 3,4,5-$OCH_3$ | O | 66 | 224 | $C_{21}H_{19}N_3O_4S$ | 409.46 | 10.26/10.22 | 0.44 | 4.81 |
| **8** | 4-Phenoxy | O | 85 | 236 | $C_{24}H_{17}N_3O_2S$ | 411.48 | 10.21/10.23 | 0.51 | 6.67 |
| **9** | 2-F | O | 95 | 318 | $C_{18}H_{12}FN_3OS$ | 337.37 | 12.46/12.39 | 0.42 | 4.61 |
| **10** | 4-F | O | 83 | 308 | $C_{18}H_{12}FN_3OS$ | 337.37 | 12.46/12.38 | 0.59 | 5.09 |
| **11** | 2-Br | O | 76 | 228 | $C_{18}H_{12}BrN_3OS$ | 398.28 | 10.55/10.56 | 0.46 | 5.33 |
| **12** | 4-Br | O | 97 | 330 | $C_{18}H_{12}BrN_3OS$ | 398.28 | 10.55/10.59 | 0.66 | 5.81 |
| **13** | 2-Cl | O | 90 | 322 | $C_{18}H_{12}ClN_3OS$ | 353.83 | 11.88/11.87 | 0.69 | 5.15 |
| **14** | 4-Cl | O | 85 | 310 | $C_{18}H_{12}ClN_3OS$ | 353.83 | 11.88/11.90 | 0.35 | 5.64 |
| **15** | 2-Cl, 5-$CF_3$ | O | 83 | 326 | $C_{19}H_{11}ClF_3N_3OS$ | 421.82 | 9.96/9.97 | 0.73 | 6.58 |
| **16** | 2-$NO_2$ | O | 80 | 304 | $C_{18}H_{12}N_4O_3S$ | 364.38 | 15.38/15.45 | 0.61 | 4.90 |
| **17** | 4-$NO_2$ | O | 88 | 294 | $C_{18}H_{12}N_4O_3S$ | 364.38 | 15.38/15.41 | 0.62 | 5.10 |
| **18** | 2-$CH_3$ | O | 90 | 320 | $C_{19}H_{15}N_3OS$ | 333.41 | 12.60/12.54 | 0.37 | 5.11 |
| **19** | 4-$CH_3$ | O | 95 | 308 | $C_{19}H_{15}N_3OS$ | 333.41 | 12.60/12.57 | 0.31 | 5.11 |
| **20** | H | S | 76 | 218 | $C_{18}H_{13}N_3S_2$ | 335.45 | 12.53/12.60 | 0.41 | 5.25 |
| **21** | 4-$OCH_3$ | S | 72 | 278 | $C_{19}H_{15}N_3OS_2$ | 365.47 | 11.50/11.43 | 0.57 | 5.20 |
| **22** | 2-$OCH_3$ | S | 65 | 256 | $C_{19}H_{15}N_3OS_2$ | 365.47 | 11.50/11.41 | 0.63 | 5.15 |
| **23** | 2-F | S | 81 | 326 | $C_{18}H_{12}FN_3S_2$ | 353.44 | 11.89/11.78 | 0.51 | 5.21 |
| **24** | 4-F | S | 66 | 292 | $C_{18}H_{12}FN_3S_2$ | 353.44 | 11.89/11.81 | 0.56 | 5.70 |
| **25** | 2-Br | S | 58 | 288 | $C_{18}H_{12}BrN_3S_2$ | 414.34 | 10.14/10.19 | 0.62 | 5.93 |
| **26** | 4-Br | S | 63 | 316 | $C_{18}H_{12}BrN_3S_2$ | 414.34 | 10.14/10.22 | 0.74 | 6.42 |
| **27** | 2-Cl | S | 77 | 312 | $C_{18}H_{12}ClN_3S_2$ | 369.89 | 11.36/11.40 | 0.78 | 5.76 |
| **28** | 4-Cl | S | 71 | 296 | $C_{18}H_{12}ClN_3S_2$ | 369.89 | 11.36/11.42 | 0.66 | 6.24 |
| **29** | 2-$NO_2$ | S | 78 | 316 | $C_{18}H_{12}N_4O_2S_2$ | 380.44 | 14.73/14.79 | 0.67 | 5.50 |
| **30** | 4-$NO_2$ | S | 82 | 288 | $C_{18}H_{12}N_4O_2S_2$ | 380.44 | 14.73/14.68 | 0.72 | 5.71 |

**Table 1** continued

| Compound | R | X | Yield (%) | M.P. (°C) | Mol. formula | Mol. weight | Nitrogen estimation (calculated/ found) | R*f*[a] | log *P*[b] |
|---|---|---|---|---|---|---|---|---|---|
| **31** | 2-$CH_3$ | S | 79 | 262 | $C_{19}H_{15}N_3S_2$ | 349.47 | 12.02/11.99 | 0.39 | 5.71 |
| **32** | 4-$CH_3$ | S | 85 | 244 | $C_{19}H_{15}N_3S_2$ | 349.47 | 12.02/11.96 | 0.43 | 5.71 |

[a] Solvent system: chloroform/ethylacetate (95:5)

[b] log *P* was generated using ACD/log *P* version 11.0 software (Advanced Chemistry Development Inc., Toronto, Canada)

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-(3,4,5-trimethoxyphenyl)urea (**7**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3378 (NH), 3052, 2936 (Ar–H), 1693 (C=O), 1629 (C=N), 1506 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.79 (s, 3H, 4-$OCH_3$), 3.88 (s, 6H, 3,5-$OCH_3$), 6.85 (s, 2H, $H_2$, $H_6$-phenyl), 7.41–7.79 (m, 5H, Ar–H), 8.53 (d, 1H, $J = 8.01$ Hz), 8.81 (s, 1H, NH), 10.56 (br s, 1H, NH); MS (FAB) *m/z* 410 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-(4-phenoxyphenyl)urea (**8**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3200 (NH), 3064, 2943 (Ar–H), 1689 (C=O), 1619 (C=N), 1503, 1488 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 6.94–7.44 (m, 13H, Ar–H), 7.90 (d, 1H, $J = 7.89$ Hz), 8.53 (d, 1H, $J = 7.98$ Hz), 8.92 (s, 1H, NH), 10.53 (br s, 1H, NH); MS (FAB) *m/z* 412 $(M + 1)^+$.

*1-(2-Fluorophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**9**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3202 (NH), 3064, 2954 (Ar–H), 1688 (C=O), 1624 (C=N), 1524 (C=C), 1105 (C–F); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.50–7.93 (m, 7H, Ar–H), 8.32 (dd, 2H, $J = 7.75$ Hz, $J = 7.94$ Hz), 8.59 (d, 1H, $J = 7.89$ Hz), 9.22 (br s, 1H, NH), 10.99 (s, 1H, NH); MS (FAB) *m/z* 338 $(M + 1)^+$.

*1-(4-Fluorophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**10**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3287 (NH), 3103 (Ar–H), 1695 (C=O), 1624 (C=N), 1508 (C=C), 1154 (C–F); $^1$H NMR (DMSO-$d_6$) $\delta$ 6.99–7.92 (m, 9H, Ar–H), 8.53 (d, 1H, $J = 7.92$ Hz), 8.92 (s, 1H, NH), 10.55 (br s, 1H, NH); MS (FAB) *m/z* 338 $(M + 1)^+$.

*1-(2-Bromophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**11**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3295 (NH), 3041, 2944 (Ar–H), 1702 (C=O), 1588 (C=N), 1503 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 6.97 (dd, 2H, $J = 7.65$ Hz, $J = 7.5$ Hz),

7.27–8.26 (m, 7H, Ar–H), 8.61 (d, 1H, $J = 7.98$ Hz), 8.87 (s, 1H, NH), 11.31 (br s, 1H, NH); MS (FAB) *m/z* 399 $(M + 1)^+$.

*1-(4-Bromophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**12**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3208 (NH), 3050, 2943 (Ar–H), 1693 (C=O), 1615 (C=N), 1486 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.14–7.88 (m, 9H, Ar–H), 8.59 (d, 1H, $J = 8.37$ Hz), 9.15 (s, 1H, NH), 10.98 (br s, 1H, NH); MS (FAB) *m/z* 399 $(M + 1)^+$.

*1-(2-Chlorophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**13**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3210 (NH), 2951 (Ar–H), 1705 (C=O), 1596 (C=N), 1443 (C=C), 733 (C–Cl); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.01 (dd, 2H, $J = 7.74$ Hz, $J = 7.55$ Hz), 7.25–7.92 (m, 6H, Ar–H), 8.32 (d, 1H, $J = 8.28$ Hz), 8.60 (d, 1H, $J = 7.98$ Hz), 9.30 (br s, 1H, NH), 11.16 (s, 1H, NH); MS (FAB) *m/z* 355 $(M + 1)^+$.

*1-(4-Chlorophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**14**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3288 (NH), 3050 (Ar–H), 1693 (C=O), 1617 (C=N), 1490 (C=C), 735 (C–Cl); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.26–7.92 (m, 9H, Ar–H), 8.52 (d, 1H, $J = 7.98$ Hz), 8.99 (s, 1H, NH), 10.52 (br s, 1H, NH); MS (FAB) *m/z* 355 $(M + 1)^+$.

*1-(2-Chloro-5-(trifluoromethyl)phenyl)-3-(naphtha[1,2-d]thiazol-2-yl)urea (**15**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3254 (NH), 3112, 2964 (Ar–H), 1695 (C=O), 1600 (C=N), 1534 (C=C), 1115, 1085 (C–F), 725 (C–Cl); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.27–7.95 (m, 8H, Ar–H), 8.59 (d, 1H, $J = 6.33$ Hz), 8.74 (s, 1H, NH), 11.52 (br s, 1H, NH); MS (FAB) *m/z* 423 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-(2-nitrophenyl)urea (**16**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3274 (NH), 3096, 2958 (Ar–H), 1697 (C=O), 1583 (C=N), 1504 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.19–7.88 (m, 6H, Ar–H), 7.96 (d, 1H, $J = 7.9$ Hz), 8.20 (d, 1H, $J = 8.37$ Hz), 8.65 (dd, 2H, $J = 8.12$ Hz, $J = 7.55$ Hz), 10.38 (s, 1H, NH), 11.99 (br s, 1H, NH); MS (FAB) *m/z* 365 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-(4-nitrophenyl)urea (**17**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3207 (NH), 3041, 2959 (Ar–H), 1708 (C=O), 1625 (C=N), 1512 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.26–7.70 (m, 7H, Ar–H), 7.93 (d, 2H, $J = 8.94$ Hz), 8.29 (d, 1H, $J = 8.01$ Hz), 9.27 (s, 1H, NH), 10.62 (br s, 1H, NH); MS (FAB) *m/z* 365 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-o-tolylurea (**18**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3248 (NH), 2964 (Ar–H), 1690 (C=O), 1615 (C=N), 1460 (C=C); $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.24 (s, 3H, $CH_3$), 7.14–7.95 (m, 9H, Ar–H), 8.51 (d, 1H, $J = 7.05$ Hz), 9.32 (s, 1H, NH), 9.95 (br s, 1H, NH); MS (FAB) *m/z* 334 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-p-tolylurea (**19**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3231 (NH), 3049, 2945 (Ar–H), 1693 (C=O), 1617 (C=N), 1514 (C=C); $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.36 (s, 3H, $CH_3$), 7.13–7.95 (m, 9H, Ar–H), 8.47 (d, 1H, $J = 6.81$ Hz), 9.24 (s, 1H, NH), 10.79 (br s, 1H, NH); MS (FAB) *m/z* 334 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-phenylthiourea (**20**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3209 (NH), 3071, 2966 (Ar–H), 1699 (C=O), 1609 (C=N), 1512 (C=C); $^1H$ NMR (DMSO-$d_6$) $\delta$ 6.50–7.78 (m, 10H, Ar–H), 7.98 (d, 1H, $J = 8.12$ Hz), 9.00 (s, 1H, NH), 10.33 (br s, 1H, NH); MS (FAB) *m/z* 336 $(M + 1)^+$.

*1-(4-Methoxyphenyl)-3-(naphtha[1,2-d]thiazol-2-yl)thiourea (**21**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3206 (NH), 3067, 2944 (Ar–H), 1702 (C=O), 1611 (C=N), 1512 (C=C); $^1H$ NMR (DMSO-$d_6$) $\delta$ 3.63 (s, 3H, $OCH_3$), 7.28 (d, 2H, $J = 7.54$ Hz), 7.38–7.88 (m, 8H, Ar–H), 8.81 (br s, 1H, NH), 9.89 (s, 1H, NH); MS (FAB) *m/z* 366 $(M + 1)^+$.

*1-(2-Methoxyphenyl)-3-(naphtha[1,2-d]thiazol-2-yl)thiourea (**22**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3207 (NH), 3117, 2956 (Ar–H), 1691 (C=O), 1611 (C=N), 1545, 1487 (C=C); $^1H$ NMR (DMSO-$d_6$) $\delta$ 3.65 (s, 3H, $OCH_3$), 6.80–7.61 (m, 6H, Ar–H), 7.88 (d, 2H, $J = 8.46$ Hz), 8.01 (d, 1H, $J = 8.54$ Hz), 8.12 (d, 1H, $J = 7.99$ Hz), 10.08 (br s, 1H, NH), 11.13 (s, 1H, NH); MS (FAB) *m/z* 366 $(M + 1)^+$.

*1-(2-Fluorophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)thiourea (**23**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3152 (NH), 3055, 2951 (Ar–H), 1708 (C=O), 1631 (C=N), 1522 (C=C), 1113 (C-F); $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.46–7.99 (m, 7H, Ar–H), 8.19 (dd, 2H, $J = 7.66$ Hz, $J = 7.56$ Hz), 8.55 (d, 1H, $J = 7.09$ Hz), 10.07 (br s, 1H, NH), 10.87 (s, 1H, NH); MS (FAB) *m/z* 354 $(M + 1)^+$.

*1-(4-Fluorophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)thiourea (**24**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3288 (NH), 3112 (Ar–H), 1705 (C=O), 1629 (C=N), 1499 (C=C), 1148 (C-F); $^1H$ NMR (DMSO-$d_6$) $\delta$ 6.87–7.95 (m, 9H, Ar–H), 8.55 (d, 1H, $J = 7.88$ Hz), 9.92 (s, 1H, NH), 10.57 (br s, 1H, NH); MS (FAB) *m/z* 354 $(M + 1)^+$.

*1-(2-Bromophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)thiourea (**25**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3313 (NH), 3075, (Ar–H), 1723 (C=O), 1616 (C=N), 1501 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 6.96–7.86 (m, 9H, Ar–H), 8.47 (d, 1H, $J = 7.98$ Hz), 8.95 (s, 1H, NH), 10.51 (br s, 1H, NH); MS (FAB) *m/z* 415 $(M + 1)^+$.

*1-(4-Bromophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)thiourea (**26**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3273 (NH), 3126 (Ar–H), 1711 (C=O), 1618 (C=N), 1487 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 6.69–7.78 (m, 9H, Ar–H), 8.43 (d, 1H, $J = 6.98$ Hz), 10.09 (s, 1H, NH), 10.72 (br s, 1H, NH); MS (FAB) *m/z* 415 $(M + 1)^+$.

*1-(2-Chlorophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)thiourea (**27**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3203 (NH), 3166, (Ar–H), 1722 (C=O), 1628 (C=N), 1522 (C=C), 778 (C–Cl); $^1$H NMR (DMSO-$d_6$) $\delta$ 6.91–7.80 (m, 9H, Ar–H), 8.23 (d, 1H, $J = 7.11$ Hz), 9.91 (s, 1H, NH), 10.68 (br s, 1H, NH); MS (FAB) *m/z* 371 $(M + 1)^+$.

*1-(4-Chlorophenyl)-3-(naphtha[1,2-d]thiazol-2-yl)thiourea (**28**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3211 (NH), 3019 (Ar–H), 1718 (C=O), 1623 (C=N), 1500 (C=C), 741 (C–Cl); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.31–8.12 (m, 9H, Ar–H), 8.67 (d, 1H, $J = 7.01$ Hz), 9.91 (s, 1H, NH), 10.11 (br s, 1H, NH); MS (FAB) *m/z* 371 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-(2-nitrophenyl)thiourea (**29**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3268 (NH), 3091, 2963 (Ar–H), 1699 (C=O), 1588 (C=N), 1501 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.20–7.94 (m, 7H, Ar–H), 8.06 (d, 1H, $J = 7.25$ Hz), 8.72 (dd, 2H, $J = 8.23$ Hz, $J = 7.48$ Hz), 10.48 (s, 1H, NH), 10.94 (br s, 1H, NH); MS (FAB) *m/z* 381 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-(4-nitrophenyl)thiourea (**30**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3200 (NH), 3058, 2941 (Ar–H), 1713 (C=O), 1631 (C=N), 1523 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.34–7.97 (m, 7H, Ar–H), 8.01 (d, 2H, $J = 8.13$ Hz), 8.18 (d, 1H, $J = 7.92$ Hz), 10.26 (s, 1H, NH), 10.69 (br s, 1H, NH); MS (FAB) *m/z* 381 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-o-tolylthiourea (**31**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3237 (NH), 2988 (Ar–H), 1700 (C=O), 1627 (C=N), 1481 (C=C); $^1$H NMR (DMSO-$d_6$) $\delta$ 2.29 (s, 3H, $CH_3$), 7.11–7.82 (m, 9H, Ar–H), 8.29 (d, 1H, $J = 7.11$ Hz), 10.02 (s, 1H, NH), 10.75 (br s, 1H, NH); MS (FAB) *m/z* 350 $(M + 1)^+$.

*1-(Naphtha[1,2-d]thiazol-2-yl)-3-p-tolylthiourea (**32**)*

IR (KBr) $\nu_{max}/cm^{-1}$ 3227 (NH), 3051, 2947 (Ar–H), 1697 (C=O), 1613 (C=N), 1516 (C=C); $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.40 (s, 3H, $CH_3$), 7.22–8.15 (m, 9H, Ar–H), 8.58 (d, 1H, $J = 7.11$ Hz), 9.87 (s, 1H, NH), 10.58 (br s, 1H, NH); MS (FAB) *m/z* 350 $(M + 1)^+$.

## Biological activity

### *Animals and drugs*

Adult male pathogen-free Swiss albino mice weighing 18–25 g were used. All animal experimentation was approved by the Animal Ethics Committee of the Institute and the procedures adhered to the National Institutes of Health (NIH) *Guidelines for the Care and Use of Laboratory Animals*. Levodopa (Sigma-Aldrich) was injected at a dose of 100 mg/kg. Haloperidol (Sigma-Aldrich) was administered at a dose of 5 mg/kg in order to induce catalepsy. Each test compound was tested at the dose of 100 mg/kg. All the drugs including synthesized compounds were suspended in 0.5% gum acacia in redistilled water and administered intraperitoneally at a volume of 0.1 ml/100 g. Thirty minutes after the administration of the levodopa and test compounds, mice were injected with haloperidol dose. Five mice were taken in each group and each mouse was used only once.

### *Measurement of catalepsy*

Haloperidol-induced catalepsy was measured with the standard bar test (Sanberg *et al*., 1988), in a wooden chamber (length 23 cm, width 10.5 cm, height 9 cm) with a horizontal metal bar (diameter 0.4 cm, length 10.5 cm) fixed at 9 cm above the floor, and at 4 cm from the back of the box. All experiments were carried out between 08:00 and 15:30 h in a room with controlled temperature (23 ± 1°C), and light intensity of 20 lux. Catalepsy was measured every 30 min during the whole session, which lasted 3 h after haloperidol injection. To measure catalepsy, the mouse was gently lifted until its forepaws firmly grasped the metal bar. Then, the mouse body was released and simultaneously a stopwatch was started. The time elapsed until the animal released both forepaws from the bar, up to a maximum of 300 s, was defined as the descent time. The sum of the descent time values measured every 30 min during the 3 h after haloperidol or vehicle was defined as the cumulative descent time (CDT[3 h]). The mean CDTs measured in animals treated by the vehicle in which haloperidol was dissolved were subtracted from the mean CDTs recorded in mice treated with haloperidol. This difference was taken as 100% of catalepsy, and served as a reference value to calculate the percent inhibition of drugs on catalepsy intensity.

*Biochemical evaluation*

Mice were sacrificed by decapitation 4 h after the last injection. The brains were quickly removed and were washed twice with ice-cold saline solution, placed into glass bottles, labeled, and stored in a deep freeze (−30°C) until processing (maximum 10 h). Tissues were homogenized in four volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.4) using a glass Teflon homogenizer (Ultra Turrax IKA T18 Basic, USA) after cutting up the brain into small pieces with scissors (for 2 min at 500 rpm). MDA and protein levels were carried out at this stage. The homogenate was then centrifuged at 10,500 × *g* for 20 min to remove nuclear debris. Clear supernatant fluid was taken and GSH-Px activity was measured at this stage. The supernatant solution was then extracted with an equal volume of an ethanol/chloroform mixture (5:3, v/v). After centrifugation at 5,000 × *g* for 30 min, the clear upper layer (the ethanol phase) was taken and used for measurement of SOD activity. All preparation procedures were performed at 4°C.

*LPO assay*

The LPO in mice brain homogenate was determined by measuring the release of thiobarbituric acid reactive substance (TBARS) in terms of MDA equivalent using a molar extinction coefficient of $1.56 \times 10^5$/min/cm as described by Ohkawa *et al.* (1979). Briefly, the homogenate was centrifuged at 3,000 × *g* for 15 min and supernatant was used for assay. Samples of 0.1 ml homogenate was mixed with 0.2 ml of 8.1% sodium dodecyl sulfate (SDS), 1.5 ml 20% glacial acetic acid, and 1.5 ml of 0.8% thiobarbituric acid (TBA). Following these additions, tubes were mixed and heated at 95°C for 1 h in a water bath and cooled under tap water before mixing 1 ml distilled water and 5 ml mixture of *n*-butanol and pyridine (15:1). The mixture was centrifuged at 2,200 × *g* for 10 min. The amount of MDA formed was measured by the absorbance of upper organic layer at a wavelength of 532 nm in Perkin Elmer spectrophotometer using appropriate controls. The results are expressed as nmol MDA/mg protein.

*GSH determination*

The amount of GSH in mice brain was measured according to the method of Sedlak and Lindsay (1968). Briefly, brain tissue was deproteinized with an equal volume of 10% trichloroacetic acid and was allowed to stand at 4°C for 2 h. The contents were centrifuged at 2000 × *g* for 15 min. The supernatant was added to 2 ml 0.4 M Tris buffer (pH 8.9) containing 0.02 M ethylene diamine tetraacetic acid (EDTA) (pH 8.9) followed by the addition of 0.01 M 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB). Finally, the mixture was diluted with 0.5 ml distilled water, to make the total mixture to 3 ml and absorbance was read in a spectrophotometer at 412 nm and results are expressed as μg GSH/g tissue.

*SOD activity determination*

Cu,Zn-SOD activity was determined according to the method of Sun *et al*. (1988). In this method, a xanthine–xanthine oxidase complex produces superoxide radicals, which react with nitrobluetetrazolium (NBT) to form the formazan compound. In brief, a reactive was prepared with 0.1 mM xanthine, 0.1 mM EDTA, 50 mg bovine serum albumin, 25 μM NBT, and 40 mM of $Na_2CO_3$ (pH 10.2). To 2.45 ml reaction volume was added 0.5 ml ethanol/chloroform (5:3, v/v) extract, previously prepared from brain homogenate. Subsequently, 50 μl 9.9 nM xanthine oxidase solution was added, the mixture was kept in a water bath of 25°C for 20 min, and the reaction was terminated using 1 ml $CuCl_2$. The absorbance of the samples was read at 560 nm. In the control sample the amount of the ethanol supernatant was replaced by the equivalent volume of phosphate-buffered saline (PBS) buffer. One unit SOD activity was defined as the amount of enzyme causing 50% inhibition of NBT reduction to formazan. SOD activity was expressed as U/mg protein.

*GSH-Px activity determination*

The GSH-Px activity was measured by the method of Paglia and Valentine (1967). The enzymatic reaction was conducted in 3 ml quartz cuvettes of 1 cm path length in a Perkin Elmer spectrophotometer. Each 3 ml assay volume contained 50 mM potassium phosphate buffer (pH 7.0), 1 mM EDTA, 1 mM sodium azide, 0.2 mM NADPH, 1 U glutathione reductase, and 1 mM reduced GSH. The sample (0.2 ml tissue homogenate), after its addition, was allowed to equilibrate for 5 min at 25°C. The reaction was initiated by adding 0.1 ml 2.5 mM $H_2O_2$. Changes in absorbance were recorded at 340 nm for 5 min. Values were expressed as units of NADPH oxidized to NADP by using the extinction coefficient of 6.22 $mM^{-1}$ $cm^{-1}$ at 340 nm. All samples were assayed in duplicate. GSH-Px activity was expressed as units per gram protein.

*Total protein determinations*

Total protein concentration of brain homogenates was determined by folin–phenol reaction as described by Lowry *et al*. (1951). The bovine serum albumin was used as a standard.

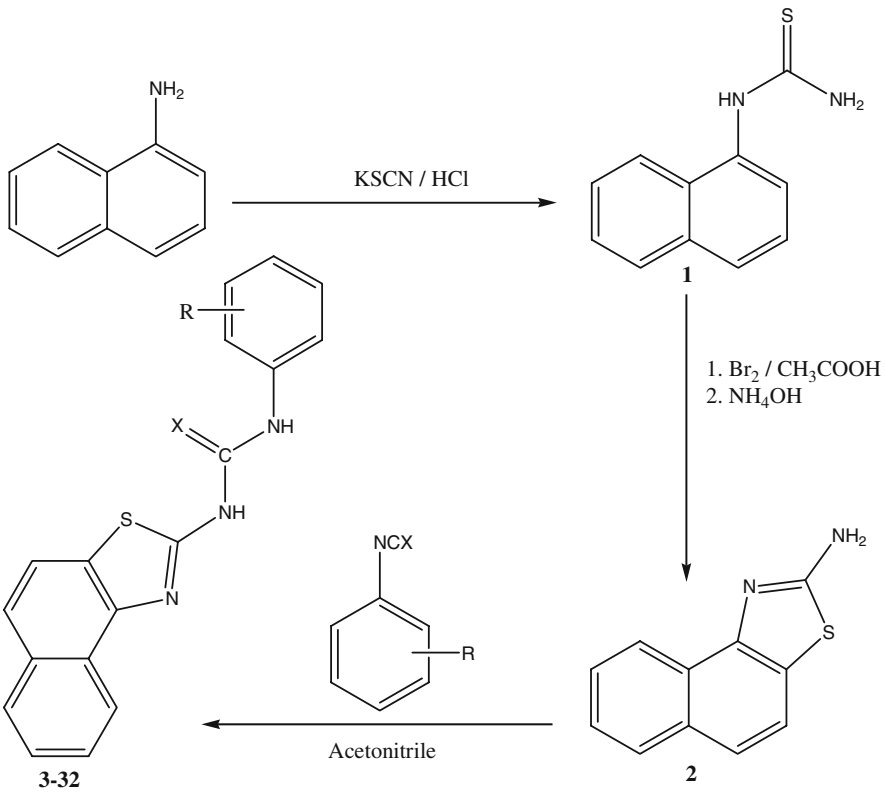
Statistical analysis

Data were expressed as the mean ± standard error (SE) of the means. For a statistical analysis of the data, group means were compared by one-way analysis of variance (ANOVA) with post hoc analysis. The post hoc Bonferroni multiple comparison test was applied to identify significance among groups. $P < 0.05$ was considered to be statistically significant.

## Results and discussion

In the present study *N*-(substituted phenyl)-*N*′-(naphtha[1,2-*d*]thiazol-2-yl)urea and thiourea derivatives (**3–32**) were synthesized as presented in Scheme 1. Naphtha[1,2-*d*]thiazol-2-amine was prepared using a literature protocol (Azam *et al*., 2008a). Compounds **3–32** were prepared by nucleophilic substitution from a primary amine, naphtha[1,2-*d*]thiazol-2-amine and the corresponding isocyanate or isothiocyanate. Reaction was carried out at room temperature in acetonitrile, and the derivatives were obtained in good yields. All compounds showed a single spot on TLC and had spectral data in accord with their anticipated structure. The physical characterization data of the urea and thiourea derivatives are given in Table 1.

There are currently a number of pharmacological models that can recapitulate many of the symptoms displayed in Parkinsonian patients such as bradykinesia, tremor, and rigidity. Catalepsy is a behavioral condition (characterized by the rigid state of a part or all of the muscle) that shares some similarity to human PD (Sanberg *et al*., 1988; Frank and Schmidt, 2003). Fairly sustained catalepsy can be induced by the dopamine $D_2$ receptor block of haloperidol (Frank and Schmidt, 2003; Moo-Puc *et al*., 2003; Marti *et al*., 2004; Vu *et al*., 2005). I employed the




**Scheme 1** Synthesis of compounds **3–32**

mouse catalepsy model to evaluate the in vivo activity of urea and thiourea derivatives. The ease of observation and the speed of the response make this assay a convenient and relatively high-throughput screen of in vivo activity. Male adult Swiss albino mice (6 weeks, 18–25 g) were injected subcutaneously with 5 mg/kg of haloperidol in order to induce catalepsy. With this type of study, a test compound was determined to be efficacious when it allowed the animals to correct the externally imposed posture within a certain time period.

All of the synthesized compounds under study revealed marked anticataleptic actions at the dose of 100 mg/kg; the mean cumulative descent time over 3 h was significantly lower ($P < 0.001$) in treated animals when compared with mice injected with haloperidol alone. Mean descent time observed at different time interval is presented in Table 2. Table 3 represents the effect of title compounds and standard drug on haloperidol-induced catalepsy in mice in terms of mean CDT[3 h] and percentage catalepsy. On comparison of anticataleptic activity of the compounds, it was observed that compounds **5**, **22**, **6**, **29**, **16**, and **7** showed better activity than standard drug levodopa. Compound **5** was the most active, whereas compound **28** was observed to be the least active among the series.

One of the major prerequisites for pharmacological screening and drug development is the prediction of absorption, for example, the transport of a molecule through cellular membranes. Drugs cross biological barriers most frequently through passive transport, which strongly depends on their lipophilicity. Therefore, hydrophobicity is one of the most important physical properties of biologically active compounds. This thermodynamic parameter describes the partitioning of a compound between an aqueous and an organic phase, and is characterized by the partition coefficient (log *P*; Avdeef, 2001; Pliska, 1996). Based on the calculated log *P* values shown in Table 1 the compounds showing significant activity in haloperidol-induced catalepsy model have partition coefficient values in the range of 4.37–6.67. A precise correlation between lipophilicity and biological activity was not observed, which reflects the interaction of title compounds with a target molecule rather than a transport phenomenon.

It can be supposed that the nitrogen atom of the naphtha[1,2-*d*]thiazol-2-amine is involved in hydrogen-bond formation (Fig. 2) based on the observation that the nitrogen atom of benzimidazole structural motif interacts with the receptor through hydrogen bonds that involve amino acids Ser 122 and Ser 141 in TM II and TM III, which are a part of the catechol binding site of the $D_2$ dopamine receptor (Teeter and DuRand, 1996; Simpson *et al*., 1999). In addition, 2-methoxy (**5**, **22**, and **6**) and 2-nitro derivatives (**29**, **16**) increase the affinities of ligands, since one additional hydrogen bond could be formed with Trp 182 (Sukalovic *et al*., 2005). It is also known that electron-attractive groups decrease the binding affinity, while electron donors such as –OMe increase the affinity for the binding at the $D_2$ dopamine receptor in comparison with the unsubstituted analogs (Homan *et al*., 1999). However, the observed activity of compounds **29** and **16** is due to an additional hydrogen-bond formation with the 2-nitro group at the receptor site as it is evident that excellent hydrogen-bonding properties are associated with nitrophenyl urea derivatives (Etter *et al*., 1990). Based on these observations proposed binding interactions of the title compounds at the receptor site are presented in Fig. 2.

**Table 2** Mean descent time observed at different time intervals

| Compound | Mean descent time (s) ± SE at time (min) | | | | | |
|---|---|---|---|---|---|---|
| | 30 | 60 | 90 | 120 | 150 | 180 |
| **3** | 72 ± 1.12[a] | 132 ± 2.34[a] | 156 ± 2.11[a] | 174 ± 3.31[a] | 172 ± 2.67[a] | 176 ± 2.19[a] |
| **4** | 41 ± 0.55[a] | 99 ± 1.43[a] | 122 ± 1.67[a] | 131 ± 2.65[a] | 136 ± 2.32[a] | 138 ± 2.47[a] |
| **5** | 11 ± 0.11[b] | 28 ± 0.54[a] | 43 ± 0.97[a] | 87 ± 0.68[b] | 109 ± 0.7[a] | 108 ± 0.57[a] |
| **6** | 32 ± 0.73[a] | 35 ± 0.34[a] | 39 ± 0.56[a] | 68 ± 1.12[b] | 120 ± 1.45[b] | 121 ± 3.59[b] |
| **7** | 29 ± 0.9[a] | 68 ± 0.88[b] | 85 ± 1.34[a] | 89 ± 2.67[a] | 107 ± 4.11[a] | 109 ± 2.38[b] |
| **8** | 76 ± 0.17[a] | 110 ± 1.32[a] | 119 ± 2.52[a] | 132 ± 5.11[a] | 135 ± 3.42[b] | 140 ± 2.09[a] |
| **9** | 57 ± 1.52[a] | 118 ± 3.12[a] | 188 ± 2.25[a] | 236 ± 3.43[b] | 245 ± 2.66[a] | 272 ± 5.12[a] |
| **10** | 84 ± 3.13[a] | 159 ± 2.14[a] | 196 ± 1.19[b] | 207 ± 4.15[a] | 226 ± 4.45[a] | 226 ± 2.22[a] |
| **11** | 77 ± 0.17[a] | 131 ± 3.15[b] | 145 ± 4.16[a] | 197 ± 3.12[a] | 219 ± 3.08[a] | 200 ± 2.34[a] |
| **12** | 82 ± 0.62[a] | 123 ± 1.12[a] | 156 ± 3.11[a] | 191 ± 2.66[a] | 214 ± 4.12[a] | 218 ± 3.19[a] |
| **13** | 59 ± 0.82[a] | 141 ± 2.56[a] | 159 ± 1.17[a] | 188 ± 4.15[a] | 211 ± 4.89[a] | 232 ± 3.35[b] |
| **14** | 78 ± 1.69[a] | 127 ± 2.85[a] | 171 ± 2.32[b] | 202 ± 2.37[a] | 199 ± 1.68[a] | 194 ± 2.59[b] |
| **15** | 67 ± 1.54[a] | 114 ± 1.62[b] | 141 ± 1.98[a] | 156 ± 2.54[a] | 150 ± 3.12[a] | 148 ± 2.33[a] |
| **16** | 19 ± 0.14[a] | 54 ± 0.15[a] | 57 ± 1.37[a] | 87 ± 2.56[a] | 98 ± 0.99[a] | 145 ± 4.57[a] |
| **17** | 51 ± 1.62[a] | 113 ± 2.65[a] | 176 ± 2.43[a] | 229 ± 2.87[a] | 245 ± 3.67[a] | 269 ± 3.48[a] |
| **18** | 71 ± 0.67[a] | 116 ± 1.11[a] | 138 ± 2.32[a] | 166 ± 2.58[b] | 170 ± 2.33[a] | 172 ± 2.72[a] |
| **19** | 69 ± 2.14[b] | 113 ± 2.54[b] | 137 ± 3.56[a] | 161 ± 2.97[a] | 168 ± 2.86[b] | 171 ± 2.32[a] |
| **20** | 65 ± 1.18[a] | 129 ± 1.99[a] | 151 ± 1.87[b] | 178 ± 2.02[a] | 174 ± 2.32[a] | 182 ± 2.88[a] |
| **21** | 44 ± 1.02[a] | 112 ± 1.65[a] | 116 ± 1.32[a] | 128 ± 2.42[a] | 129 ± 2.51[b] | 145 ± 2.97[a] |
| **22** | 19 ± 0.22[a] | 44 ± 0.76[a] | 65 ± 0.74[a] | 87 ± 1.76[a] | 98 ± 1.83[b] | 95 ± 1.91[a] |
| **23** | 57 ± 0.96[b] | 143 ± 2.54[a] | 152 ± 2.67[a] | 183 ± 2.33[a] | 206 ± 3.52[b] | 234 ± 3.98[a] |
| **24** | 43 ± 1.91[a] | 98 ± 2.73[a] | 167 ± 2.18[b] | 246 ± 2.39[b] | 232 ± 2.84[a] | 241 ± 2.79[a] |
| **25** | 83 ± 1.72[b] | 160 ± 2.56[a] | 189 ± 3.73[a] | 207 ± 2.97[a] | 223 ± 3.57[b] | 226 ± 3.53[a] |
| **26** | 57 ± 1.01[a] | 139 ± 2.98[a] | 161 ± 2.75[a] | 222 ± 3.47[a] | 223 ± 4.76[a] | 220 ± 4.87[a] |
| **27** | 69 ± 2.34[a] | 156 ± 3.55[b] | 173 ± 4.12[a] | 190 ± 3.39[a] | 189 ± 2.17[a] | 186 ± 2.66[a] |
| **28** | 92 ± 1.8[a] | 169 ± 1.94[a] | 198 ± 2.37[a] | 216 ± 2.85[a] | 232 ± 3.55[b] | 228 ± 3.12[a] |
| **29** | 20 ± 0.09[a] | 36 ± 0.57[a] | 71 ± 0.92[a] | 88 ± 1.13[a] | 109 ± 1.98[a] | 122 ± 1.58[a] |
| **30** | 77 ± 1.14[b] | 178 ± 2.56[a] | 199 ± 3.76[a] | 201 ± 3.83[a] | 207 ± 3.54[b] | 208 ± 4.61[a] |
| **31** | 68 ± 1.37[a] | 110 ± 2.48[a] | 138 ± 3.37[a] | 157 ± 3.78[a] | 160 ± 2.59[a] | 166 ± 2.36[a] |
| **32** | 72 ± 1.23[a] | 114 ± 2.12[a] | 136 ± 1.98[a] | 161 ± 2.77[a] | 173 ± 2.35[a] | 172 ± 2.39[a] |
| **Control** | 6 ± 0.06 | 4 ± 0.11 | 5 ± 0.1 | 5 ± 0.07 | 6 ± 0.53 | 7 ± 0.54 |
| **Haloperidol** | 176 ± 3.69[c] | 217 ± 4.43[c] | 268 ± 3.88[c] | 300 ± 4.63[c] | 300 ± 4.19[c] | 300 ± 4.76[c] |
| **Levodopa** | 32 ± 0.16[a] | 49 ± 0.46[a] | 99 ± 2.15[a] | 119 ± 1.87[a] | 122 ± 2.17[a] | 137 ± 2.26[a] |

Data are presented as mean descent time (s) ± SE. Number of animals per group ($n$) = 5. Haloperidol 5 mg/kg. Compounds **3**–**32** and levodopa at the dose of 100 mg/kg 30 min prior to haloperidol injection. Data was analyzed by one-way ANOVA followed by Bonferroni post hoc analysis

[a] $P < 0.001$ as compared with haloperidol group

[b] $P < 0.01$ as compared with haloperidol group

[c] $P < 0.001$ as compared with control group

**Table 3** Effect of test compounds (**3–32**) and standard drug on haloperidol-induced catalepsy in mice in terms of mean CDT[3h] and percentage catalepsy

| Compound | Mean CDT[3h] ± SE | Catalepsy (%) | Reduction in catalepsy (%) |
|---|---|---|---|
| **3** | 882 ± 6.05[a] | 55.56 | 44.44 |
| **4** | 667 ± 3.93[a] | 41.49 | 58.51 |
| **5** | 386 ± 2.61[a] | 23.1 | 76.9 |
| **6** | 415 ± 2.99[a] | 25 | 75 |
| **7** | 487 ± 4.61[a] | 29.71 | 70.29 |
| **8** | 712 ± 3.99[a] | 44.44 | 55.56 |
| **9** | 1116 ± 2.45[a] | 70.88 | 29.12 |
| **10** | 1098 ± 4.6[a] | 69.7 | 30.3 |
| **11** | 969 ± 3.55[a] | 61.26 | 38.74 |
| **12** | 984 ± 2.98[a] | 62.24 | 37.76 |
| **13** | 990 ± 2.85[a] | 62.63 | 37.37 |
| **14** | 971 ± 2.41[a] | 61.39 | 38.61 |
| **15** | 776 ± 4.68[a] | 48.63 | 51.37 |
| **16** | 460 ± 3.21[a] | 27.95 | 72.05 |
| **17** | 1083 ± 5.10[a] | 68.72 | 31.28 |
| **18** | 833 ± 3.34[a] | 52.36 | 47.64 |
| **19** | 819 ± 3.47[a] | 51.44 | 48.56 |
| **20** | 879 ± 4.11[a] | 55.37 | 44.63 |
| **21** | 674 ± 4.42[a] | 41.95 | 58.05 |
| **22** | 408 ± 3.18[a] | 24.54 | 75.46 |
| **23** | 975 ± 2.92[a] | 61.65 | 38.35 |
| **24** | 1027 ± 2.49[a] | 65.05 | 34.95 |
| **25** | 1088 ± 2.19[a] | 69.04 | 30.96 |
| **26** | 1022 ± 5.48[a] | 64.73 | 35.27 |
| **27** | 963 ± 1.28[a] | 60.86 | 39.14 |
| **28** | 1135 ± 3.93[a] | 72.12 | 27.88 |
| **29** | 446 ± 2.24[a] | 27.03 | 72.97 |
| **30** | 1070 ± 3.03[a] | 67.87 | 32.13 |
| **31** | 799 ± 3.60[a] | 50.13 | 49.87 |
| **32** | 828 ± 2.47[a] | 52.03 | 47.97 |
| **Control** | 33 ± 1.34 | – | – |
| **Haloperidol** | 1561 ± 5.61[b] | 100 | – |
| **Levodopa** | 558 ± 2.05[a] | 34.36 | 65.64 |

Data are presented as mean cumulative descent time (s) ± SE. Number of animals per group ($n$) = 5. The sum of the descent time values measured every 30 min during the 3 h after haloperidol or vehicle is defined as the cumulative descent time (CDT[3h]). Compounds **3–32** and levodopa administered i.p. 30 min prior to haloperidol injection. Data were analyzed by one-way ANOVA followed by Bonferroni post hoc analysis. [a] $P < 0.001$ as compared with haloperidol group. [b] $P < 0.001$ as compared with control group

Oxidative stress and products of LPO are implicated in the pathophysiology of various neurodegenerative diseases (Jenner, 2003). Treatment of animals with haloperidol has been found to increase oxidative stress by altering the levels of

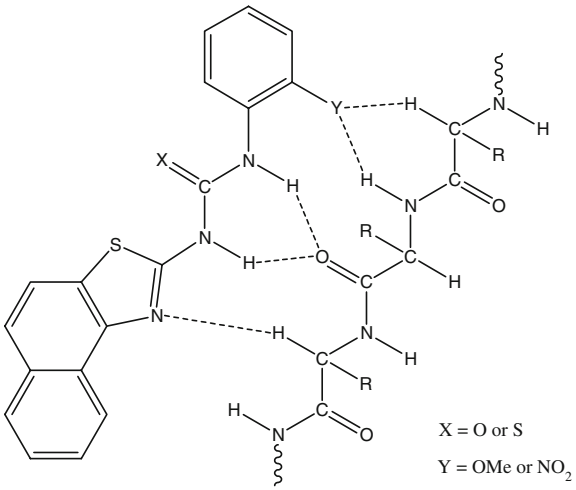



**Fig. 2** Proposed interaction of the title compounds at the binding site

antioxidant enzymes, and to cause oxidative injury in the brain (Parikh *et al.*, 2003). Furthermore, it may exacerbate the oxidative stress by increased oxidative dopamine metabolism following dopamine receptor blockade (Cadet and Brannock, 1998) as well as by its oxidative biotransformation to produce a potentially neurotoxic pyridinium metabolite (haloperidol$^{+}$) in rat brain (Subramanyam *et al.*, 1990). MDA is a reflection of LPO, whereas GSH, GSH-Px, and SOD are important antioxidant defense agents. In the present study, some active compounds (**5**, **6**, **22**, and **29**) were selected for the measurement of antioxidant enzyme activities from the brain homogenate to highlight the role of title compounds in suppressing the catalepsy and oxidative stress induced by haloperidol administration.

The elevated level of MDA indicates increased free-radical generation in the haloperidol-treated mice. Haloperidol-induced increment in MDA content of the brain tissue was significantly prevented by the pretreatment with compounds **5**, **6**, **22**, and **29** ($P < 0.001$). This observation is in accordance with data from the literature showing increased MDA levels in the brain of haloperidol-treated rats (Burger *et al.*, 2005). The antioxidant enzymes catalase and GSH-Px detoxify $H_2O_2$ by converting it to $O_2$ and $H_2O$ (Maddipati and Marnett, 1987; Vendemiale *et al.*, 1999). In addition, to help detoxify ROS, biological antioxidants, including GSH, α-tocopherol, carotenoids, and ascorbic acid, will react with most oxidants. Similarly, in the present study, a consistent decrease of GSH level, and SOD and GSH-Px activities in haloperidol-treated mice is an indication of impaired synthesis of GSH and degradation of antioxidant enzymes by free radicals during detoxification processes. It appears that increased levels of ROS are not detoxified in haloperidol-treated mice due to decreased efficiency of antioxidant enzymatic and nonenzymatic mechanisms, and may act as mediators of neuronal damage. Compounds **5**, **6**, **22**, and **29** administered prior to haloperidol suppressed these effects, restoring GSH level and antioxidant enzymes (SOD and GSH-Px) activities to almost similar levels to in control. These results are summarized in Table 4. The present findings are in

**Table 4** Biochemical estimation from brain homogenate

| Compound | LPO (nmol MDA/ mg protein) | GSH μg/g tissue | GSH-Px (U/g protein) | SOD (U/mg protein) |
|---|---|---|---|---|
| **5** | 2.504 ± 0.50[a] | 16.764 ± 0.26[a] | 1.622 ± 0.05[a] | 1.833 ± 0.07[a] |
| **6** | 2.706 ± 0.10[a] | 13.582 ± 1.02[a] | 1.469 ± 0.05[a] | 1.609 ± 0.03[c] |
| **22** | 2.045 ± 0.08[a] | 13.096 ± 0.98[a] | 1.684 ± 0.04[a] | 2.105 ± 0.09[a] |
| **29** | 3.226 ± 0.25[a] | 12.452 ± 0.65[a] | 1.398 ± 0.28[a] | 1.769 ± 0.12[a] |
| **Haloperidol** | 4.728 ± 0.19[b] | 6.854 ± 0.15[b] | 1.102 ± 0.04[b] | 1.141 ± 0.07[b] |
| **Control** | 1.157 ± 0.06 | 23.45 ± 0.23 | 1.794 ± 0.03 | 2.129 ± 0.06 |

The data are expressed as mean ± SE ($n = 5$)

[a] $P < 0.001$ compared with corresponding value for haloperidol-treated mice

[b] $P < 0.001$ compared with corresponding value for control mice

[c] $P < 0.01$ compared with corresponding value for haloperidol-treated mice

agreement with earlier studies, which reported changes in levels of some antioxidant enzyme activity after haloperidol treatment (Parikh *et al.*, 2003).

In summary, I have developed a new series of *N*-(substituted phenyl)-*N*′-(naphtha[1,2-*d*]thiazol-2-yl)urea and thiourea derivatives that are active against Parkinsonian symptoms induced by haloperidol in mice. These compounds are effective in decreasing the elevated levels of MDA while restoring cellular defense mechanisms such as GSH content as well as GSH-Px and SOD activities in haloperidol-treated mice, suggesting the role of free radicals in the pathophysiology of haloperidol-induced catalepsy and possible antioxidant action of title compounds. Our recent results with the naphtha[1,2-*d*]thiazol-2-amine moiety have given impetus to the present investigation.

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