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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Antidepressant activity of carbamates and urea derivatives

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Abstract Thirteen (13) compounds of *N*-phenyl-*O*-alkyl carbamates (**1** and **3**), *N*,*N*-diethyl-*N*′-alkyl/aryl/phenylpiperazinoureas (**4–6**, **8–12**), *N*-phenyl-*N*′-phenylpiperazino/imidazoureas (**2**, **7**), and *N*-ethyl-(*N*′-phenylpiperazino) thioureas **13** were synthesized and tested for their antidepressant-like activity in mice. It was found that compound *N*-phenyl-*O*-heptyl carbamate **1** and *N*-phenyl-*N*′-phenylpiperazinourea **2** showed 32.5 and 27.7% antidepressant activity in the forced swim test in mice, respectively. Considering other carbamates it was found that a decrease in alkyl chain length caused a marked decline in the antidepressant activity. Compounds **1–4** show even higher activities in the forced swim test than the standard phenelzine.

Keywords Antidepressant · Carbamates · Urea derivatives · Forced swim test · Thiourea

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Introduction

In recent years, psychiatrics focused their research on the discovery of more efficient drugs for depressive disorders having also fewer side effects. Depression is a chronic illness just like diabetes or asthma. There are many factors which can trigger depression, such as being out of job, very serious illness, i.e., cancer, HIV etc., divorce, flunking out of school, loss in business. Sometimes there is no apparent factor that triggers a depression. There are many prescription drugs that can cause depression; fortunately, depression is a highly treatable condition. However, to alleviate the depressant, antidepressants are normally taken as a medication.

MAOIs (monoamine oxidase inhibitors), tricyclic, and tetracyclic compounds are commonly used as antidepressants. These medications are very popular among the psychiatrists and in general practitioners. Unsatisfactory efficiency and unfavorable side effects alert the scientist to search for better therapeutic antidepressant drugs. Antidepressants are often used for the treatment of anxiety, bipolar, and eating disorders or chronic pain. Antidepressant drugs change the mood of patients from poignant to happiness and are therefore often referred to as "mood brighteners".

Dibenzocycloheptenes and related classes of tricyclic compounds are well known for their antidepressant activity (Stach, 1969; Bloom and Tretter, 1969; Siegismund and Friedrich, 1970; Burg and Delobelle, 1970; Traber and Horstmann, 1990; Epling *et al*., 1988; Hoffsommer *et al*., 1962). Sertraline, escitalopram, fluxetine, and venlafaxine are commonly prescribed antidepressants in the US since 2005 (Czygan, 2003). Newly developed antidepressants, (serotonin syndrome) possess harmful effects resulting from the overstimulation of serotonin receptors. Selective

Serotonin Reuptake Inhibitor (SSRI) medication is now very common in use, but unexpected discontinuation may result in both, somatic and psychological withdrawal symptoms. Therefore, novel antidepressant medications lacking these drawbacks are needed.

A series of urea compounds are natural products with important biological activities (Fournier *et al*., 1991). Besides, they are used as dyes for cellulose fiber, antioxidants in gasoline, corrosion inhibitors, agricultural pesticides, herbicides, and antitumors (Fournier *et al*., 1991; Bigi *et al*., 2000; Takahiro *et al*., 1987). Several unsymmetrical ureas are known for their efficient pharmaceutical and herbicidal effects (Groszek, 2002; Yonova and Stoilkova, 2005). Potent antiglycation and antidepressant activities were reported for a series of symmetrical and unsymmetrical disubstituted ureas (Khan *et al*., 2009; Perveen *et al*., 2011).

Symmetrical and urea derivatives are used as drug precursors, such as HIV protease inhibitor, CCK-β receptor, endothelin antagonist, and have cytokinin activity, HDL-elevating, antiviral, antifungal, analgesic, and insect control properties (Lam *et al*., 1994; Castro *et al*., 1996; von Geldern *et al*., 1996; Bruce and Zwar, 1966; Struga *et al*., 2007; Daniel *et al*., 2005; Miesel, 1981; Richardson and Whittle, 1984). Aryl urea derivatives are considered to have therapeutic agents for inflammatory and/or immunomodulatory diseases by the inhibition of p38 kinase (Ranges *et al*., 2002). Tetrasubstituted urea derivatives are considered as cholinergic (Butler *et al*., 1988). In the present study, the antidepressant effect of carbamates and a series of 1,3-disubstituted and trisubstituted urea derivatives are reported.

Results and discussions

Two carbamates **1** and **3** were synthesized by the reaction of heptanol and ethanol with phenyl isocyanate (Scheme 1), and the urea derivatives **4–6** and **8–12** by the reaction of *p*-carboxyaniline, *p*-chloroaniline, *o*-carboxyaniline, 1-phenylpiperazine, *m*-carboxyaniline, aniline, *N*,*N*-dimethylethylene diamine, and 2,6-dimethylaniline, respectively, with *N*,*N*-diethylcarbamyl chloride (Scheme 2). Compounds **2** and **7** were prepared by the reaction of phenyl isocyanate with 1-phenylpiperazine and imidazole, respectively (Scheme 3). *N*-Ethyl-*N*′-phenylpiperazino thiourea **13** was prepared by treating 1-phenylpiperazine with ethyl thiocyanate (Scheme 4).

The compounds **1–13** were tested for antidepressant activity in mice using the forced swim test protocol (Porsolt *et al*., 1978; Dar and Khatoon, 1997). The compound *N*-phenyl-*O*-heptyl carbamate **1** showed 32.5% of immobility inhibition, the highest % inhibition in immobility time in mice as compared to the reference drug phenelzine.

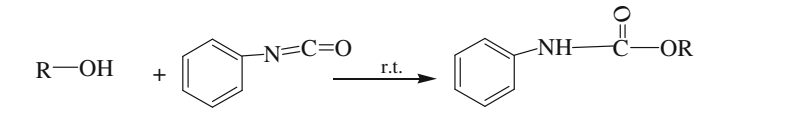
N-Phenyl-*N*′-phenylpiperazinourea **2**, *N*-phenyl-*O*-ethyl carbamate **3**, and *N*,*N*-diethyl-*N*′-(*p*-carboxyphenyl)urea **4** showed also considerable antidepressant activity, 27.7, 21.6, and 16.7%, respectively. Comparison of the antidepressant activities of compounds **1** and **3** (Table 1) indicates that the activity of the compounds increases with prolongation of the non-polar side chain (Perveen *et al*., 2010). For the *N*,*N*-diethyl-*N*′-(*p*-carboxyphenyl)urea **4** an antidepressant activity of 16.7% was determined, while its *o*-analog **6** shows only 3.5% antidepressant activity. The increase of the antidepressant activity from the *meta* to the *ortho* to the *para* analog (**9–6–4**) (Perveen *et al*., 2011) seems to be caused by the decrease of the steric hindrance of the carboxyl group and the positive charge imposed on C-2 and C-6 position by the carboxyl group in *meta* position **9** (Table 1). *N*,*N*-diethyl-*N*′-substituted ureas seem to be less potent antidepressants than *N*′-monoalkyl/aryl derivatives as is demonstrated by the comparison of the activities of compound **8** (15.5%) with that of **2** (27.7%). No activity was found for the thiourea compound *N*-ethyl-*N*′-phenylpiperazino thiourea **13** which has an ethyl group instead of a phenyl or diethyl group at the nitrogen of urea bridge. In *N*,*N*-diethyl-*N*′-(*p*-chlorophenyl)urea **5** a chloro group is attached at *para* position of the phenyl ring which is not a strong electron-withdrawing group as compared to the carboxyl group in compound **4** (Perveen *et al*., 2011). This makes compound **5** less antidepressant (7.04%); substitution of the *para* position in compounds **5** and **4** by hydrogen further reduces electronic effects in the aromatic ring, which causes a further reduction of the antidepressant activity. A very enhanced depressant activity was found for the compound *N*-phenyl-*N*′-imidazourea **7** (60.8%), two structural properties may cause this strong biological effect, first, the proton, attached to the nitrogen of the urea bridge which causes less steric hindrance compared to an alkyl or aryl group, and second the imidazole moiety the nitrogens of which may form hydrogen bridges with receptors.

Experimental

General

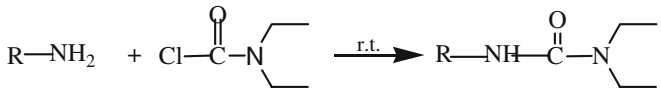
Ethanol and heptyl alcohol were dried by using magnesium turning. 1-phenylpiperazine, imidazole, *o*-,*m*-,*p*-aminobenzoic acid, *p*-chloroaniline, aniline, *N*,*N*-dimethylethylene diamine, phenyl isocyanate, ethyl thiocyanate, and diethylcarbamyl chloride were of reagent grade (Merck, Darmstadt) and used directly without purification. IR

Scheme 1 Synthetic route for the preparation of carbamates



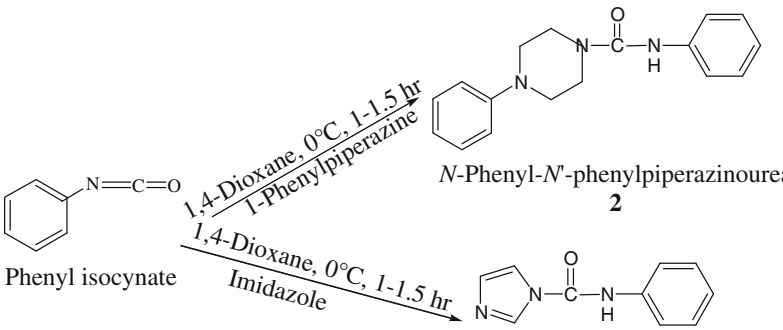
R = heptyl/ethyl Phenyl isocyanate *N*-Phenyl-*O*-heptyl/ethyl carbamate **1, 3**

Scheme 2 Synthetic route for the preparation of **4–6**, **8–12**



R= alkyl/aryl/ 1-phenylpiperazine Diethylcarbamyl chloride *N*,*N*-Diethyl-*N*′-alkyl/aryl/phenylpiperazinoureas **4-6**, **8-12**

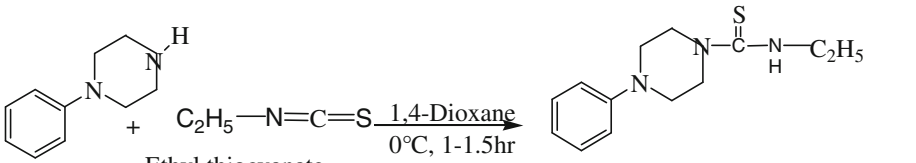
Scheme 3 Synthetic route for the preparation of compounds **2** and **7**



Phenyl isocynate *N*-Phenyl-*N*′-phenylpiperazinourea **2**

N-Phenyl-*N*′-imidazourea **7**

Scheme 4 Synthetic route for the preparation of compound **13**



Ethyl thiocyanate

1-Phenylpiperazine *N*-Ethyl-*N*′-phenylpiperazino thiourea **13**

spectroscopic analysis was carried out using a FT IR spectrophotometer (Avatar 320) equipped with a Smart Specul ATR Thermospectra Tech 035-603 for liquids, and a Thermo Spectra-Tech 035-703 for solids. The values are reported in cm^{-1}. The ^1H NMR spectroscopy was performed on a Bruker AC 400 (400 MHz) spectrometer and the values are reported in δ (ppm). TMS was taken as internal standard. EI MS spectra were recorded on a Finnigan-MAT-311A apparatus and the values are reported in *m/z*.

*General procedure for the preparation of carbamates (**1** and **3**)*

0.1 mol (11.9 g) of phenyl isocyanate was treated with 0.7 mol heptanol at room temperature and the progress of reaction was monitored by TLC. The TLC showed that a single product was formed. After completion of the reaction, the mixture was poured into ice-cold water with continuous stirring. The solid obtained was filtered, dried, and afforded pure *N*-phenyl-*O*-heptyl carbamate **1** in quantitative yields (Scheme 1). While in the case of ethanol, two products were formed after purification by column chromatography afforded, *N*-phenyl-*O*-ethyl carbamate **3** and symmetrical 1,3-disubstituted ureas (Scheme 1).

*N-Phenyl-O-heptyl carbamate **1*** Recrystallized from cyclohexane (Yield 95%). mp 205–207 °C. ^1H NMR ($CDCl_3$) δ; 8.40 (1H, br.s, NH), 7.42–7.25 (4H, m, $H^{2,3,5,6}$), 7.08 (1H, m, H^4), 3.84 (2H, t, $J = 6.8$ Hz, CH_2), 1.72–1.64 (2H, m, CH_2), 1.30–1.21 (8H, m, $4CH_2$), 0.84 (3H, t, $J = 9.0$ Hz, CH_3)—EI MS: *m/z* (rel. abund. %), 235 (M^+, 21), 220 (13), 206 (36), 136 (55), 119 (87), 77 (45)—Anal.: Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 9.00; N, 5.95%. Found: C, 71.49; H, 8.89; N, 5. 97%.

*N-Phenyl-O-ethyl carbamate **3*** Recrystallized from cyclohexane (Yield 40%). mp 58–60 °C. ^1H NMR ($CDCl_3$)

Table 1 % Inhibition immobilities compared to standard phenelzine of synthesized *N*-phenyl-*O*-alkyl carbamates, *N*,*N*-diethyl-*N*'-alkyl/aryl/phenylpiperazinoureas, *N*-phenyl-*N*'-phenylpiperazino/imidazoureas and *N*-ethyl-*N*'-phenylpiperazino thiourea (**1**–**13**)

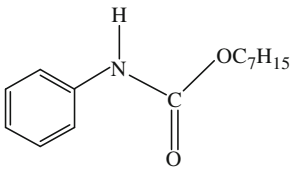
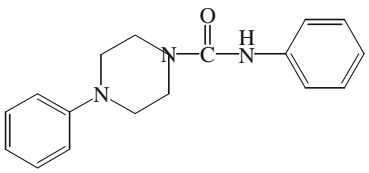
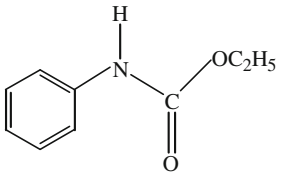
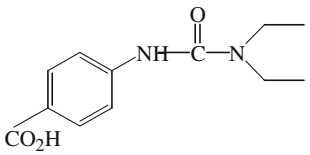
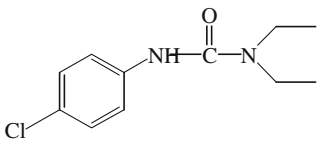
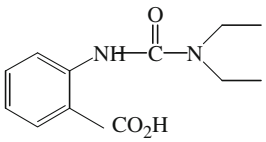
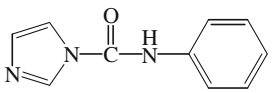
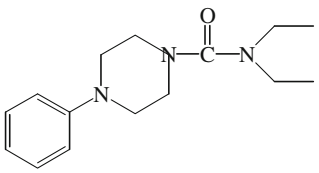
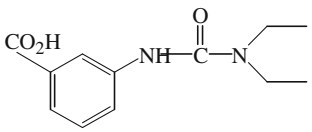
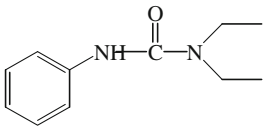
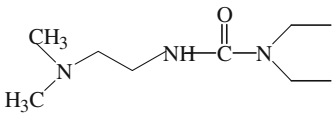
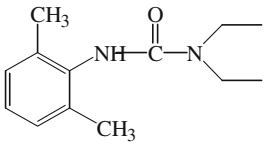
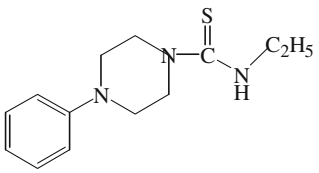
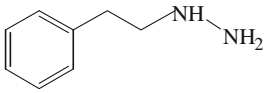
Sr. #.	Compound	Structure	Yield %	% Inhibition immobility
1	*N*-Phenyl-*O*-heptyl carbamate		95	32.5%↓
2	*N*-Phenyl-*N*-phenylpiperazinourea		93	27.7%↓
3	*N*-Phenyl-*O*-ethyl carbamate		40	21.6%↓
4	*N*,*N*-Diethyl-*N*′-(*p*-carboxyphenyl)urea		86	16.74%↓
5	*N*,*N*-Diethyl-*N*′-(*p*-chlorophenyl)urea		85	7.04%↓
6	*N*,*N*-Diethyl-*N*′-(*o*-carboxyphenyl)urea		78	3.52%↓
7	*N*-Phenyl-*N*′-imidazourea		87	60.8%↑
8	*N*,*N*-Diethyl-*N*′-phenylpiperazinourea		91	15.5%↑
9	*N*,*N*-Diethyl-*N*′-(*m*-carboxyphenyl)urea		88	6.87%↑

Table 1 continued

Sr. #.	Compound	Structure	Yield %	% Inhibition immobility
10	*N*,*N*-Diethyl-*N*′-phenylurea		96	6.6%↑
11	*N*,*N*-Diethyl-*N*′-ethylene(*N*′′, *N*′′-dimethyl)urea		80	1.76%↑
12	*N*,*N*-Diethyl-*N*′-(2,6-dimethylphenyl)urea		90	Nil
13	*N*-Ethyl-*N*′-phenylpiperazino thiourea		84	Nil
14	Phenelzine			15.9%↓

↓ % Inhibition immobility

↑ % Increase immobility

δ; 8.36 (1H, br.s, NH), 7.40–7.27 (4H, m, $H^{2,3,5,6}$), 7.05 (1H, m, H^4), 4.12 (2H, q, $J = 9.0$ Hz, CH_2), 1.25 (3H, t, $J = 9.0$ Hz, CH_3)—EI MS: *m*/*z* (rel. abund. %); 165 (M^+, 87), 150 (49), 136 (27), 119 (100), 77 (34)—Anal.: Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48%. Found: C, 65.51; H, 6.67; N, 8.44%.

Preparation of N-phenyl-N′-phenylpiperazinourea **2** *and N-phenyl-N′-imidazourea* **7**

For the preparation of **2** and **7**, to a mixture of (0.7 mol) 1-phenylpiperazine/imidazole in 20–25 mL of 1, 4-dioxane was added at 0 °C dropwise neat 10.85 mL (11.9 g, 0.1 mol) phenyl isocyanate. The reaction mixture was then allowed to stir at room temperature for 1–1.5 h. After completion of the reaction (TLC analysis), the mixture was poured into ice-cold water yielding fine crystals of *N*-phenyl-*N*′-phenylpiperazinourea **2** and *N*-phenyl-*N*′-imidazourea **7** (Scheme 3).

N-Phenyl-N′-phenylpiperazinourea **2** Recrystallized from hexane (Yield 93%). mp 280 °C ^{1}H NMR ($CDCl_3$) δ; 8.15 (2H, d, $J = 9.0$ Hz, $H^{2,6}$), 8.00 (1H, br.s, NH), 7.32 (2H, dd, $J = 9.0$, 2.5 Hz, $H^{3,5}$), 7.03 (1H, m, H^4), 7.67 (2H, dd, $J_{3',2'\,=\,5',6'} = 8.0$, $J_{3',4'\,=\,5',4'} = 7.2$ Hz, $H^{3',5'}$), 6.97 (2H, d, $J_{2',3'\,=\,6',5'} = 8.0$ Hz, $H^{2',6'}$), 6.82 (1H, t, $J_{4',(3',5')} = 7.2$ Hz, $H^{4'}$), 3.61 (4H, t, $J_{1'',2''} = 4.8$ Hz, $2CH_2$), 3.15 (4H, t, $J_{2'',1''} = 4.8$ Hz, $2CH_2$)—EI MS: *m*/*z* (rel. abund. %); 281 (M^+, 8), 204 (56), 189 (16), 161 (43), 119 (100), 77 (98)—Anal.: Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94%. Found: C, 72.53; H, 6.87; N, 14.89%.

N-Phenyl-N′-imidazourea **7** Recrystallized from hexane (Yield 87%). ^{1}H NMR (DMSO-d_6) δ; 10.12 (1H, s, NH), 7.98 (1H, dd, $J_{2,4} = 2.1$, $J_{2,5} = 1.5$ Hz, H^2), 7.84 (1H, dd, $J_{5,4} = 4.1$, $J_{5,2} = 1.5$ Hz, H^5), 7.63–7.58 (2H, m, $H^{2\prime}/H^{6\prime}$), 7.35–7.30 (2H, m, $H^{3\prime}/H^{5\prime}$), 6.86–6.77 (1H, m, $H^{4\prime}$), 6.61 (1H, dd, $J_{4,5} = 4.1$, $J_{4,2} = 2.1$ Hz, H^4);—EI MS: *m*/*z* (rel. abund. %); 187 (M^+, 8), 120 (10), 110 (46), 77 (100)—Anal.: Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45%. Found: C, 64.14; H, 4.86; N, 22.47%.

General procedure for the preparation of N,N-diethyl-N′-alkyl/aryl/phenylpiperazinoureas ***4–6*** *and* ***8–12***

To a solution of (0.7 mol) aryl/alkylamine/phenylpiperazine, *N*, *N*-diethylcarbamyl chloride was added dropwise (Scheme 2) at room temperature with continuous stirring.

Progress of reaction was monitored via TLC (Mukund *et al*., 2004). After completion of reaction the reaction mixture was purified with hexane, then evaporated in vacuo and the resultant solid residue was crystallized from an appropriate solvent to afford the pure derivatives **4–6** and **8–12**, respectively.

N,N-Diethyl-N′-(p-carboxyphenyl)urea ***4*** Recrystallized from hexane (Yield 86%). ^{1}H NMR ($CDCl_3$) δ; 9.52 (2H, br.s, NH/OH), 7.63 (2H, d, $J = 9.0$ Hz, $H^{3,5}$), 6.74 (2H, d, $J = 9.0$ Hz, $H^{2,6}$), 3.03 (4H, q, $J = 7.1$ Hz, $2CH_2$), 0.98 (6H, t, $J = 7.1$ Hz, $2CH_3$)—EI MS: *m/z* (rel. abund. %); 236 (M^+, 23), 121 (35), 207 (12), 192 (16), 136 (18)—Anal.: Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86%. Found: C, 61.15; H, 6.72; N, 11.79%.

N,N-Diethyl N′1-(4-chlorophenyl)urea ***5*** Recrystallized from hexane (Yield 85%). ^{1}H NMR ($CDCl_3$) δ; 7.45 (2H, d, $J = 8.8$ Hz, $H^{3,5}$), 7.26 (2H d, $J = 8.8$ Hz, $H^{2,6}$), 4.82 (1H, br.s, NH), 3.04 (4H, q, $J = 7.3$ Hz, $2CH_2$), 1.31 (6H, t, $J = 7.3$ Hz, $2CH_3$)—EI MS: *m/z* (rel. abund. %); 228 (M^{+2}, 2), 226 (M^+, 7), 211 (4), 197 (20), 154 (10)—Anal.: Calcd for $C_{11}H_{15}N_2OCl$: C, 58.28; H, 6.67; N, 12.36%. Found: C, 58.301; H, 6.71; N, 12.44%.

N,N-Diethyl-N′-(o-carboxyphenyl)urea ***6*** Recrystallized from hexane (Yield 78%). ^{1}H NMR ($CDCl_3$) δ; 9.86 (2H, br.s, NH/OH), 8.05 (1H, dd, $J = 7.7$, 1.7 Hz, H^3), 7.79 (1H, dd, $J = 7.7$, 1.5 Hz, H^6), 7.33 (1H, t, $J = 7.7$ Hz, H^4), 7.24 (1H, t, $J = 7.7$ Hz, H^5), 3.01 (4H, q, $J = 7.0$ Hz, $2CH_2$), 0.99 (6H, t, $J = 7.0$ Hz, $2CH_3$)—EI MS: *m/z* (rel. abund. %); 236 (M^+, 25), 121 (30), 207 (10), 192 (18), 136 (15)—Anal.: Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86%. Found: C, 61.21; H, 6.89; N, 11.67%.

N,N-Diethyl-N′-phenylpiperazinourea ***8*** Recrystallized from hexane (Yield 91%). mp 251 °C. ^{1}H NMR ($CDCl_3$) δ; 7.21 (1H, t, $J_{4,(3,5)} = 7.2$ Hz, H^4), 7.10 (2H, d, $J_{2,3\ =\ 6,5} = 7.2$ Hz, $H^{2,6}$), 6.93 (2H, t, $J_{3,(4,2)\ =\ 5,(4,6)} = 7.2$ Hz, $H^{3,5}$), 3.47 (8H, br.s, $4CH_2$), 2.32 (4H, br.s, $2CH_2$), 1.53 (6H, br.s, $2CH_3$)—EI MS: *m/z* (rel. abund. %); 261 (M^+, 16), 246 (35), 232 (21), 189 (29), 184 (35)—Anal.: Calcd for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08%. Found: C, 68.97; H, 8.94; N, 16.11%.

N,N-Diethyl-N′-(m-carboxyphenyl)urea ***9*** Recrystallized from hexane (Yield 88%). ^{1}H NMR ($CDCl_3$) δ; 8.02 (1H, td, $J = 7.7$, 1.2 Hz, H^4), 7.95 (1H, m, H^2), 7.61 (1H, t, $J = 7.7$ Hz, H^5), 7.53 (1H, td, $J = 7.7$, 1.2 Hz, H^6), 3.03 (4H, q, $J = 7.3$ Hz, $2CH_2$), 1.29 (6H, t, $J = 7.3$ Hz, $2CH_3$)—EI MS: *m/z* (rel. abund. %), 236 (M^+, 86), 207 (15), 192 (95), 152 (82)—Anal.: Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86%. Found: C, 61.11; H, 6.74; N, 11.75%.

N,N-Diethyl-N′-phenylurea ***10*** Recrystallized from hexane (Yield 96%). mp 80–82 °C. ^{1}H NMR ($CDCl_3$) δ; 7.48 (2H, dd, $J = 8.0$, 1.2 Hz, $H^{2,6}$), 7.26 (2H, ddd, $J = 8.0$, 7.6, 1.0 Hz, $H^{3,5}$), 6.97 (1H, dd, $J = 7.6$, 1.2 Hz, H^4), 5.81 (1H, br.s., NH), 3.32 (2H, q, $J = 7.0$ Hz, CH_2), 3.16 (2H, q, $J = 7.1$ Hz, CH_2), 1.15 (3H, t, $J = 7.0$ Hz, CH_3), 1.1 (3H, t, $J = 7.1$ Hz, CH_3)—IR ν_{max} cm^{-1} (KBr): 3294, 2950, 2931, 1643, 1599, 1500, 1442, 1316, 1236—EI MS: *m/z* (rel. abund. %); 192 (M^+, 19), 177 (33), 163 (39), 134 (55), 100 (82), 92 (78), 77 (100)—Anal.: Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57%. Found: C, 68.66; H, 8.32; N, 14.52%.

N,N-Diethyl-N′-ethylene-(N″,N″-dimethyl)urea ***11*** Recrystallized from hexane (Yield 80%). ^{1}H NMR ($CDCl_3$) δ; 5.48 (br.s., 1H, NH), 3.70 (6H, br.s, $2CH_3$), 3.41 (2H, t, $J = 5.2$ Hz, CH_2), 3.19 (4H, q, $J = 7.2$ Hz, $2CH_2$), 3.10 (2H, t, $J = 5.2$ Hz, $2CH_2$), 0.88 (6H, t, $J = 7.2$ Hz, $2CH_3$)—EI MS: *m/z* (rel. abund. %), 187 (M^+, 40), 159 (12), 128 (95)—Anal.: Calcd for $C_9H_{21}N_3O$: C, 57.72; H, 11.30; N, 22.44%. Found: C, 57.62; H, 11.50; N, 22.35%.

N,N-Diethyl-N′-(2, 6-dimethylphenyl)urea ***12*** Recrystallized from hexane (Yield 90%). mp 357 °C. ^{1}H NMR ($CDCl_3$) δ; 8.30 (1H, br.s, NH), 7.03 (3H, m, Ar–H), 3.29 (6H, s, $2CH_3$), 2.49 (4H, br.s, $2CH_2$), 2.22 (6H, br.s, $2CH_3$)—EI MS: *m/z* (rel. abund. %); 220 (M^+, 37), 205 (28), 191 (47),), 148 (33), 147 (100), 116 (85)—Anal.: Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72%. Found: C, 70.82; H, 9.19; N, 12.75%.

Preparation of N-ethyl-N′-phenylpiperazino thiourea ***13*** For the preparation of **13** (Scheme 4), to a mixture of 1-phenylpiperazine (0.7 mol) in 20–25 mL of 1,4-dioxane was added at 0 °C dropwise neat 8.60 mL (8.7 g, 0.1 mol) ethyl thiocyanate. The reaction mixture was then allowed to stir at room temperature for 1–1.5 h. After completion of the reaction (TLC analysis), the mixture was poured into ice-cold water yielding fine crystals of *N*-ethyl-*N′*-phenyl-piperazino thiourea **13**.

Recrystallized from hexane (Yield 84%). ^{1}H NMR ($CDCl_3$) δ; 7.66 (2H, dd, $J_{3',2'\ =\ 5',6'} = 8.1$, $J_{3',4'\ =\ 5',4'} = 7.0$ Hz, $H^{3',5'}$), 6.97 (2H, d, $J_{2',3'\ =\ 6',5'} = 8.1$ Hz, $H^{2',6'}$), 6.81 (1H, t, $J_{4',(3',5')} = 7.0$ Hz, $H^{4'}$), 3.60 (4H, t, $J_{1'',2''} = 4.9$ Hz, $2CH_2$), 3.42 (2H, q, $J = 7.0$ Hz, CH_2), 3.17 (4H, t, $J_{2'',1''} = 4.9$ Hz, $2CH_2$), 0.99 (3H, t, $J = 7.0$ Hz, CH_3)—EI MS: *m/z* (rel. abund. %); 249 (M^+, 19), 234 (34), 220 (26), 205 (74), 162 (100)—Anal.: Calcd for $C_{13}H_{19}N_3S$: C, 62.61; H, 7.68; N, 16.85%. Found: C, 62.66; H, 7.62; N, 16.81%.

Anti-depressant test (forced swim test in mice) FST

Mice (20–30 g) of either sex were taken to perform the pre-test session by placing them in a FST tank (glass tank; height = 25 cm, diameter = 15 cm), filled with water of 25 °C up to the height of 15 cm for 15 min. Movement of animals were noted carefully. Injured or ill animals, e.g., those showing symptoms of nose bleeding are discarded. Animals received phenelzine as standard antidepressant

drug (10 mg/kg) or compounds **1**–**13**, respectively, at a dose of 10 mg/kg dissolved in 10% DMSO. After 1 h the animals were placed in the FST tank and the immobility times were determined in seconds for 5 min using a stop watch. In control animals, only vehicle (10 mL of 10% DMSO in water, used also to solubilize the drugs) was administered at otherwise analogous conditions as mentioned above. Percent reduction in immobility time is calculated as follows:

$$\% \text{ Reduction} = \left(\text{Mean immobility time of test mouse} / \text{Mean immobility time of control x } 100\right) - 100$$

Conclusion

Comparing the antidepressant activities of *N*-phenyl-*O*-heptyl carbamate **1** and *N*-phenyl-*O*-ethyl carbamate **3** indicates that the activity of the compounds increases with prolongation of the non-polar side chain. Second, the antidepressant activity of urea derivatives increases with the presences of a strong electron-withdrawing group at *para* position of phenyl ring. Compound *N*-phenyl-*N*′-imidazourea **7** has reverse activity, it increase the depression to the animal.

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