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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of new piperidyl indanone derivatives as anticonvulsant agents

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Abstract A series of 5,6-dimethoxy-2-{1-[arylamino/alkylamino(thioxo)methyl]-4-piperidyl-methyl}-1-indanones (**4a–l**) were designed and synthesized by the reaction of 5,6-dimethoxy-2-(piperidin-4-yl-methyl)-indan-1-one with aryl/alkyl isothiocyanates. The anticonvulsant activity was evaluated in animal models by maximal electroshock seizure and subcutaneous pentylenetetrazole tests. The neurotoxic effects were assessed by rotorod and ethanol potentiation tests. Gamma amino butyric acid (GABA) estimation of the selected compounds was performed in rat brain utilizing UV absorbance data. Compounds **4d**, **4g**, and **4j** displayed encouraging anticonvulsant profile against both seizure models with remarkably lower neurotoxicity. These compounds were found to increase the GABA level in rat brain significantly.

Keywords Indanone · Piperidine · Thioamide · Anticonvulsant activity · GABA estimation

Introduction

Epileptic seizures have been recognized for millennia. One of the earliest descriptions of a secondarily generalized tonic-clonic seizure was recorded over 3000 years ago in Mesopotamia. And now it is the second most common chronic neurological disorder characterized by recurrent seizures. The term epilepsy is used when recurrent spontaneous seizures occur. The different types of epilepsy are not based on a single underlying mechanism but are multifactorial in origin. It results from abnormal and sudden discharge of cerebral neurons. In considerable number of epilepsies genetic or familial disposition also plays an important role in seizure precipitation. Overwhelming evidences indicate that imbalance between inhibitory (gamma amino butyric acid (GABA), adenosine) and excitatory (glutamate, aspartate) neurotransmitters in the central nervous system (CNS) is a main cause underlying seizure initiation, propagation, and amplification in both experimental and clinical conditions (Luszczki *et al.*, 2006; Dudek and Spitz, 1997; Meldrum, 2000; Parsons *et al.*, 1998; Pearl and Gibson, 2004; Sherwin, 1999; Treiman, 2001).

At present, modern therapeutic approaches to control seizure attacks in epileptic patients are based on increase in GABA content in the brain, blocking voltage-dependent neuronal Na channels and reducing the excitatory neurotransmission (Coyle, 1997; Loscher and Schmidt, 2004).

Previously, we have reported several heterocyclic compounds (benzimidazoles, benzothiazol-2-yl thiadiazoles, benzothiazoles, semicarbazones etc.) showing considerable anticonvulsant activity (Siddiqui *et al.*, 2007a, b, 2009a, b; Rana *et al.*, 2008). In the course of our investigations on heterocyclic moieties as new anticonvulsants, a number of piperidyl indanone moiety of thioamide derivatives have been synthesized based on reported earlier work (Hinko *et al.*, 1996). Recently, it was found that some nipecotic acid derivatives containing the piperidine moiety exhibited anticonvulsant activity by GABA uptake inhibitory mechanism (Zhang *et al.*, 2007). In the light of the

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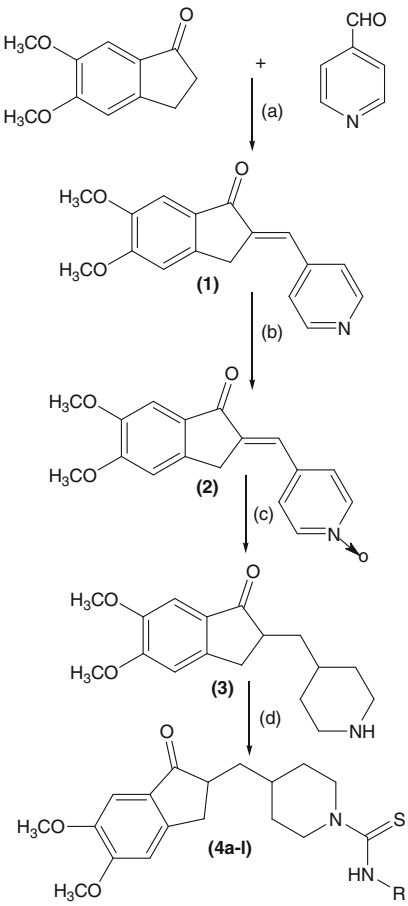

R = C_6H_5, 2-CH_3.C_6H_4 , 3-CH_3.C_6H_4, 4-CH_3.C_6H_4, 2-NO_2.C_6H_4, 3-NO_2.C_6H_4, 4-NO_2.C_6H_4, 2-Cl.C_6H_4, 3-Cl.C_6H_4, 4-Cl.C_6H_4, n-C_3H_7, n-C_4H_9

Scheme 1 Reagents and Conditions: (*a*) *p*-toluene sulfonic acid, toluene, reflux; (*b*) hydrogen peroxide, acetic acid; (*c*) H_2, Pd/C; (*d*) RNCS, ethanol, reflux

above discussions we have synthesized new Piperidyl Indanone derivatives and evaluated them for anticonvulsant activity via possible GABA-ergic pathways (Scheme 1).

Materials and methods

Chemistry

Melting points were taken in open capillary tubes and are uncorrected. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a Bruker model DRX 400 NMR spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on BIO-RAD FTS 135 spectrometer in KBr pellet. Elemental analysis was performed using CHNS Elimentar (Analysen systime, GmbH) Germany Vario EL III. TLC was carried out using silica gel 60 F_{254} plates (Merck). All the chemicals and solvents used were obtained from Merck.

*(2E)-5,6-dimethoxy-2-(pyridin-4-yl-methylene)indan-1-one (**1**)*

The synthesis of 5,6-dimethoxy-2-(pyridin-4-yl-methylene)indan-1-one (**1**) was carried out according to the procedure reported elsewhere (U. S. Patent 1997).

*N-oxide of 5,6-dimethoxy-2-(pyridin-4-yl-methylene)indan-1-one (**2**)*

To a solution of 5,6-dimethoxy-2-(pyridin-4-yl-methylene)-indan-1-one (**1**) (2.81 g, 0.01 mol) in acetic acid, 5-ml hydrogen peroxide was added and heated the reaction mixture at 45–50°C for about 2–3 h. The mixture was cooled and poured over crushed ice to give a yellow colored solid. Yield: 75%; m.p: 160–164°C. log *P* 4.52; % CHN found (calculated): C 72.58 (70.90), H 5.37 (4.68), N 4.98 (4.50). IR (KBr) cm^{-1}: 2970 (C–H), 1655 (C=O), 1620 (C=N), 1560 (C=C). ^{1}H NMR (δppm): 1.14–1.38 (d, $J = 12.3$ Hz, 1H, H-3′ piper.), 1.82–1.89 (d, $J = 12.8$ Hz, 1H, H-5′ piper), 2.32–2.37 (d, $J = 8.7$ Hz, 1H, H-2′piper.), 2.42–2.81 (d, $J = 12.5$ Hz, 1H, H-6′ piper.), 3.21 (s, 2H, indan.), 3.24 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 6.46 (s, 1H, Ar–H), 6.73 (s, 1H, Ar–H). 8.12 (s, 1H, alip).

*(2E)-5,6-dimethoxy-2-(piperidin-4-yl-methyl)indan-1-one (**3**)*

N-oxide of 5,6-dimethoxy-2-(pyridin-4-yl-methylene)indan-1-one (**2**) (2.97 g, 0.01 mol) was dissolved in 20 ml of methanol in dichloromethane solution (5:95). A catalytic amount of Pd/C (500 mg) was added to the reaction mixture and refluxed (75–80°C) for 8 h under 10 kg/cm^2 pressure. The mixture was cooled, filtered over silica moistened with MeOH/water mixture. The filtrate was distilled under vacuum to give white colored powder. Yield: 77%; m.p: 152–157°C. log *P* 4.36; % CHN found (calculated): C 70.56 (69.98), H 8.01 (7.99), N 4.84 (4.50); IR (KBr) cm^{-1}: 3385 (N–H), 3036 (C–H), 1725 (C=O), ^{1}H NMR (δppm): 0.88–0.91 (t, $J = 10.2$ Hz, 1H, aliph.), 1.06–1.23 (dd, $J = 14.1$, 13.0 Hz, 2H, H-3′ piper.), 1.40–1.47 (t, $J = 10.1$ Hz, 1H, aliph.), 1.46 (bs, 1H, H-4′ piper.), 1.67–1.93 (dd, $J = 13.4$, 13.7 Hz, 2H, H-5′ piper), 2.23–2.42 (t, $J = 9.4$ Hz, 2H, H-2′piper.), 2.32–2.47 (m, 1H, NH), 2.71 (bs, IH, indan.), 2.91–2.97 (t, $J = 13.8$ Hz, 2H, H-6′ piper.), 3.32–3.36 (t, $J = 12.6$ Hz, 2H, indan.), 3.46 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 6.21 (s, 1H, Ar–H), 6.35 (s, 1H, Ar–H).

*General procedure for the synthesis of compounds **4a–l***

An equimolar mixture of 5,6-dimethoxy-2-(piperidin-4-yl-methyl)indan-1-one (**3**) (2.89 g, 0.01 mol) and aryl/alkyl isothiocyanates were refluxed in absolute ethanol for 4–6 h. The reaction mixture was allowed to cool gradually to room temperature. The solid product obtained was filtered, washed with petroleum ether, dried, and recrystallized from ethanol.

2-[1-Anilino(thioxo)methyl-4-piperidyl-methyl]-5,6-dimethoxy-1-indanone (**4a**) Yield 76%; mp 154–156°C; log *P* 4.12; %CHN found (calculated): C 68.17 (67.90), H 6.67 (6.65), N 6.63 (6.60); IR (KBr) cm^{-1}: 3488 (N–H), 3044 (C–H), 1713 (C=O), 1020 (C=S); ^{1}H NMR (δppm): 0.89–0.94 (t, $J = 10.2$ Hz, 1H, aliph.), 1.17–1.34 (dd, $J = 13.2$, 12.0 Hz, 2H, H-3′ piper.), 1.38–1.43 (t, $J = 9.6$ Hz, 1H, aliph.), 1.54 (bs, 1H, H-4′ piper.), 1.71–1.83 (dd, $J = 13.2$, 13.2 Hz, 2H, H-5′ piper), 2.04–2.08 (t, $J = 8.4$ Hz, 2H, H-2′piper.), 2.62 (bs, IH, indan.), 2.85–2.92 (t, $J = 13.6$ Hz, 2H, H-6′ piper.), 3.31-3.37 (t, $J = 11.6$ Hz, 2H, indan.), 3.43 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 6.25 (s, 1H, Ar–H), 6.36 (s, 1H, Ar–H), 7.18–7.43 (m, 5H, Ar–H), 7.82 (s, 1H, NH–Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 27.46, 28.98, 31.52, 32.49, 36.93, 43.91, 44.58, 55.04, 55.69, 102.64, 107.07, 114.52, 121.85, 147.81, 150.93, 152.32, 154.98, 156.28, 183.58, 210.66.

5,6-Dimethoxy-2-[1-thioxo(2-toluidino)methyl-4-piperidyl-methyl]-1-indanone (**4b**) Yield 79%; mp 142–144°C; log *P*: 4.58; %CHN found (calculated): C 68.73 (68.46), H 6.91 (6.89), N 6.41 (6.39); IR (KBr) cm^{-1}: 3236 (N–H), 3019 (C–H), 1683 (C=O), 1035 (C=S); ^{1}H NMR (δppm): 0.99-1.05 (t, $J = 11.8$ Hz, 1H, aliph.), 1.12–1.25 (dd, $J = 12.8$, 12 Hz, 2H, H-3′ piper.), 1.37–1.41 (t, $J = 8.2$ Hz, 1H, aliph.), 1.61 (bs, 1H, H-4′ piper.), 1.87–1.99 (dd, $J = 12.6$, 12.6 Hz, 2H,, H-5′ piper.), 2.12–2.16 (t, $J = 8.2$ Hz, 2H, H-2′ piper.), 2.29 (s, 3H, CH_3), 2.63–2.69 (t, $J = 12.2$ Hz, 2H, H-6′piper.), 2.75–2.81 (t, $J = 11.8$ Hz, 2H, indan.), 3.38 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 6.35 (s, 1H, Ar–H), 6.39 (s, 1H, Ar–H), 6.84–7.05 (m, 2H, Ar–H), 7.12–7.33 (m, 2H, Ar–H), 7.78 (s, 1H, NH-Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 17.90, 27.87, 29.06, 31.52, 32.58, 36.93, 44.12, 44.69, 55.04 55.69, 103.53, 106.88, 115.12, 122.06, 147.81, 151.11, 151.98, 155.23, 155.98, 184.05, 209.96.

5,6-Dimethoxy-2-[1-thioxo(3-toluidino)methyl-4-piperidyl-methyl]-1-indanone (**4c**) Yield 67%; mp 178–180°C; log *P*: 4.58; %CHN found (calculated): C 68.43 (68.46), H 6.84 (6.89), N 6.34 (6.39); IR (KBr) cm^{-1}: 3468 (N–H), 2911 (C–H), 1726 (C=O), 1029 (C=S); ^{1}H NMR (δppm): 0.86–0.92 (t, $J = 10.4$ Hz, 1H, aliph.), 1.15–1.21 (dd, $J = 13.2$, 12.0 Hz, 2H, H-3′ piper.), 1.37–1.42 (t, $J = 10.2$ Hz, 1H, aliph.), 1.59 (bs, 1H, H-4′ piper.), 1.94–1.82 (dd, $J = 13.2$, 13.2 Hz, 2H, H-5′piper.), 2.05–2.09 (t, $J = 8.4$ Hz, 2H, H-2′ piper.), 2.28 (s, 3H, CH_3), 2.53 (bs, 1H,, indan.), 2.68–2.74 (t, $J = 12.2$ Hz, 2H, H-6′piper.), 3.33–3.38 (t, $J = 10.3$ Hz, 2H, indan), 3.45 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 6.28 (s, 1H, Ar–H), 6.39 (s, 1H, Ar–H), 7.15–7.40 (m, 3H, Ar–H), 7.52–7.63 (m, 1H, Ar–H) 7.88 (s, 1H, NH–Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 20.69, 27.52, 28.98, 31.52, 32.49, 36.93, 43.91, 44.58, 55.04, 55.69, 102.64, 109.07, 115.66, 123.45 147.81, 149.52, 151.69, 154.81, 156.28, 184.09, 210.66.

5,6-Dimethoxy-2-[1-thioxo(4-toluidino)methyl-4-piperidyl-methyl]-1-indanone (**4d**) Yield 73%; mp 165–167°C; log P:4.58; %CHN found (calculated): C 68.51 (68.46), H 6.84 (6.89), N 6.41 (6.39); IR (KBr) cm^{-1}: 3554 (N–H), 2909 (C–H), 1765 (C=O), 1039 (C=S); ^{1}H NMR (δppm): 0.92-0.98 (t, $J = 10.4$ Hz, 1H, aliph.), 1.11–1.24 (dd, $J = 13.2$, 12.0 Hz, 2H, H-3′ piper.), 1.35–1.39 (t, $J = 8.4$ Hz, 1H, aliph.), 1.62 (bs, 1H, H-4′piper.) 1.73–1.81 (dd, $J = 13.2$, 13.2 Hz, 2H, H-5′ piper.), 2.11–2.15 (t, $J = 8.4$ Hz, 2H, H-2′ piper.), 2.23 (s, 3H, CH_3), 2.69 (bs, 1H, indan.), 2.70–2.77 (t, $J = 13.4$ Hz, 2H, H-6'piper), 3.43 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 6.23 (s, 1H, Ar–H), 6.35 (s, 1H, Ar–H), 7.19–7.21 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.28–7.30 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.82 (s, 1H, NH–Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 21.00, 27.46, 28.98, 31.52, 32.49, 36.93, 43.91, 44.58, 55.04, 55.69, 102.64, 109.68, 114.52, 125.51, 148.12, 150.93, 151.69, 154.98, 156.28, 184.58, 209.96.

5,6-Dimethoxy-2-{1-[2-nitroanilino(thioxo)methyl]-4-piperidyl-methyl}-1-indanone (**4e**) Yield 51%; mp 139–141°C; log *P*:4.37; %CHN found (calculated): C 61.43 (61.39), H 5.84 (5.80), N 8.97 (8.95); IR (KBr) cm^{-1}: 3447 (N–H), 2988 (C–H), 1665 (C=O), 1043 (C=S); ^{1}H NMR (δppm): 0.98–1.03 (t, $J = 10.2$ Hz, 1H, aliph.), 1.18–1.30 (dd, $J = 13.2$, 12.0 Hz, 2H, H-3′ piper.), 1.39–1.44 (t, $J = 9.62$ Hz, 1H, aliph.), 1.52 (bs, 1H, H-4′ piper.), 2.05–2.17 (dd, $J = 13.2$, 13.2 Hz, 2H, H-5′piper.), 2.59-2.63 (t, $J = 8.4$ Hz, 2H, H-2′piper.), 2.72 (bs, 1H, indan.), 2.86–2.93 (t, $J = 13.4$ Hz, 2H, H-6′piper.), 3.32–3.38 (t, $J = 11.4$ Hz, 2H, indan.), 3.44 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 6.26 (s, 1H, Ar–H), 6.37 (s, 1H, Ar–H), 7.18–7.20 (d, $J = 8.2$ Hz, 1H, Ar–H), 7.28–7.29 (m, 3H, Ar–H), 8.52 (s, 1H, NH–Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 27.46, 28.98, 31.52, 32.49, 36.93, 43.91, 44.58, 55.15, 55.77, 102.64, 107.07, 115.35, 122.68, 148.92, 151.69, 152.32, 154.98, 156.28, 184.40, 211.65.

5,6-Dimethoxy-2-{1-[3-nitroanilino(thioxo)methyl]-4-piperidyl-methyl}-1-indanone (**4f**) Yield 59%; mp 151-153°C; log *P*:4.51; %CHN found (calculated): C 61.41 (61.39), H 5.82 (5.80), N 8.92 (8.95); IR (KBr) cm^{-1}: 3311 (N–H), 3073 (C–H), 1709 (C=O), 1036

(C=S); ^{1}H NMR (δppm): 0.91-0.95 (t, J = 9.6 Hz, 1H, aliph.), 1.24–1.36 (dd, J = 13.2, 13.2 Hz, 2H, H-3′ piper.), 1.40–1.45 (t, J = 9.6 Hz, 1H, aliph.), 1.63 (bs, 1H, H-4′ piper.), 1.98–2.10 (dd, J = 13.2, 13.2 Hz, 2H, H-5′piper.), 2.61–2.65 (t, J = 8.4 Hz, 2H, H-2′piper.), 2.65 (bs, IH, indan.), 2.88–2.95 (t, J = 13.6 Hz, 2H, H-6′piper.), 3.33–3.39 (t, J = 11.6 Hz, 2H, indan.), 3.45 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 6.28 (s, 1H, Ar–H), 6.38 (s, 1H, Ar–H), 7.09 (s, 1H, Ar–H), 7.25–7.28 (d, J = 8.1 Hz, 1H, Ar–H), 7.31–7.33 (d, J = 8.1 Hz, 1H, Ar–H), 7.39–7.41 (d, J = 8.1 Hz, 1H, Ar–H), 8.83 (s, 1H, NH–Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 27.46, 28.98, 31.52, 32.49, 36.93, 43.91, 44.58, 55.15, 55.77, 102.64, 107.07, 113.38, 120.96, 146.35, 151.08, 151.93, 155.12, 156.28, 184.40, 211.65.

5,6-Dimethoxy-2-{1-[4-nitroanilino(thioxo)methyl]-4-piperidyl-methyl}-1-indanone (**4g**) Yield 67%; mp 163-165°C; log P: 4.58; %CHN found (calculated): C 61.33 (61.39), H 5.78 (5.80), N 8.92 (8.95); IR (KBr) cm^{-1}: 3448 (N–H), 3047 (C–H), 1676 (C=O), 1053 (C=S); ^{1}H NMR (δppm): 0.96–1.02 (t, J = 10.2 Hz, 1H, aliph.), 1.26–1.38 (dd, J = 13.2, 12.4 Hz, 2H, H-3′ piper.), 1.42–1.47 (t, J = 9.6 Hz, 1H, aliph.), 1.58 (bs, 1H, H-4′ piper.), 2.01–2.12 (dd, J = 13.2, 13.2 Hz, 2H, H-5′ piper), 2.61–2.66 (t, J = 8.4 Hz, 1H, H-2′piper.), 2.62 (bs 1H, indan.), 2.89–2.96 (t, J = 13.6 Hz, 2H, H-6′piper.), 3.36–3.42 (t, J = 11.6 Hz, 2H, indan.), 3.47 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 6.29 (s, 1H, Ar–H), 6.41 (s, 1H, Ar–H), 7.43–7.45 (d, J = 8.6 Hz, 2H, Ar–H), 7.52–7.54 (d, J = 8.6 Hz, 1H, Ar–H), 8.94 (s, 1H, NH–Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 27.46, 28.98, 31.52, 32.49, 36.93, 43.91, 44.58, 55.15, 55.77, 102.64, 107.07, 113.38, 121.46, 147.81, 150.08, 151.93, 154.98, 156.42, 184.40, 211.65.

2-{1-[2-Chloroanilino(thioxo)methyl]-4-piperidyl-methyl}-5,6-dimethoxy-1-indanone (**4h**) Yield 71%; mp 172–174°C; log *P*:4.63; %CHN found (calculated): C 62.81 (62.80), H 5.95 (5.93), N 6.17 (6.10); IR (KBr) cm^{-1}: 3443 (N–H), 2922 (C–H), 1653 (C=O), 1059 (C=S); ^{1}H NMR (δppm): 0.85–0.91 (t, J = 10.4 Hz, 1H, aliph.), 1.16–1.28 (dd, J = 13.2, 12.2 Hz, 2H, H-3′ piper.), 1.36–1.41 (t, J = 9.4 Hz, 1H, aliph.), 1.69(bs, 1H, H-4′ piper.), 1.99–2.11 (dd, J = 13.2, 12.2 Hz, 2H, indan.), 2.56-2.61 (t, J = 8.4 Hz, 2H, H-2′piper.), 2.69 (bs, IH, indan.), 2.83–2.90 (t, J = 13.6 Hz, 2H, H-6′piper.), 3.32-3.38 (t, J = 11.6 Hz, 2H, indan.), 3.45 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 6.29 (s, 1H, Ar–H), 6.37 (s, 1H, Ar–H), 7.34–7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.54–7.68 (m, 3H, Ar–H), 8.36 (s, 1H, NH–Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 27.55, 28.98, 31.52, 32.49, 36.93, 43.91, 44.67, 53.40, 55.08, 102.64, 107.07, 115.63, 121.77, 148.92, 149.52, 151.69, 154.98, 156.86, 185.13, 210.98.

2-{1-[3-Chloroanilino(thioxo)methyl]-4-piperidyl-methyl}-5,6-dimethoxy-indanone (**4i**) Yield 76%; mp 160–162°C; log *P*: 5.15; %CHN found (calculated): C 62.77 (62.80), H 5.94 (5.93), N 6.13 (6.10); IR (KBr) cm^{-1}: 3430 (N–H), 2995 (C–H), 1725 (C=O), 1042 (C=S); ^{1}H NMR (δppm): 0.94–0.99 (t, J = 10.4 Hz, 1H, aliph.), 1.27–1.39 (dd, J = 13.2, 13.2 Hz, 2H, H-3′ piper.), 1.43–1.48 (t, J = 9.6 Hz, 1H, aliph.), 1.66 (bs, 1H, H-4′ piper.), 2.09–2.20 (dd, J = 13.2, 13.2 Hz, 2H, H-5′piper.), 2.61–2.66 (t, J = 8.4 Hz, 2H, H-2′piper.), 2.70 (bs, 1H, indan.), 2.89–2.96 (t, J = 13.6 Hz, 2H, H-6′piper.), 3.36–3.42 (t, J = 11.4 Hz, 2H, indan.), 3.48 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 6.41 (s, 1H, Ar–H), 6.49 (s, 1H, Ar–H), 7.53–7.59 (m, 1H, Ar–H), 7.61–7.69 (m, 2H, Ar–H), 7.72–7.74 (m, 1H, Ar–H), 8.72 (s, 1H, NH–Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 27.46, 28.98, 31.52, 32.49, 36.93, 43.91, 44.58, 53.40, 55.08, 102.64, 107.07, 116.44, 122.68, 149.14, 150.75, 152.84, 154.98, 156.86, 185.13, 210.98.

2-{1-[4-Chloroanilino(thioxo)methyl]-4-piperidyl-methyl}-5,6-dimethoxy-indanone (**4j**) Yield 80%; mp 169–171°C; log *P*: 5.11; %CHN found (calculated): C 62.78 (62.80), H 5.91 (5.93), N 6.14 (6.10); IR (KBr) cm^{-1}: 3421 (N–H), 3022 (C–H), 1732 (C=O), 1049 (C=S); ^{1}H NMR (δppm): 1.03–1.08 (t, J = 10.2 Hz, 1H, aliph.), 1.17–1.29 (dd, J = 13.2, 12.4 Hz, 2H, H-3′ piper.), 1.43–1.48 (t, J = 9.6 Hz, 1H, aliph.), 1.68 (bs, 1H, H-4′ piper.), 1.99–2.11 (dd, J = 13.2, 13.2 Hz, 2H, H-5′piper.), 2.60–2.65 (t, J = 8.4 Hz, 1H, H-2′piper.), 2.71 (bs, 1H, indan.), 2.82–2.89 (t, J = 13.4 Hz, 2H, H-6′piper.), 3.35–3.41 (t, J = 11.4 Hz, 2H, indan), 3.45 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 6.39 (s, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 7.64–7.65 (d, J = 8.7 Hz, 2H, Ar–H), 7.72–7.74 (d, J = 8.1 Hz, 2H, Ar–H), 8.87 (s, 1H, NH–Ar, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 27.46, 28.98, 31.52, 32.49, 36.93, 43.91, 44.58, 55.04, 55.69, 102.64, 107.07, 119.38, 124.46, 149.76, 150.93, 153.32, 154.98, 156.28, 185.13, 210.98.

5,6-Dimethoxy-2-{1-[propylamino(thioxo)methyl]-4-piperidyl-methyl}-1-indanone (**4k**) Yield 62%; mp 114–116°C; log *P*: 3.43; %CHN found (calculated): C 64.42 (64.59), H 7.71 (7.74), N 7.12 (7.17); IR (KBr) cm^{-1}: 3428 (N–H), 2972 (C–H), 1709 (C=O), 1056 (C=S); ^{1}H NMR (δppm): 0.83-0.89 (t J = 10.4 Hz, 1H, aliph.), 0.97–0.99 (t, J = 7.6 Hz, 3H, CH_3), 1.00–1.12 (dd, J = 13.2, 12.4 Hz, 2H, H-3′ piper.), 1.28–1.33 (t, J = 9.6 Hz, 1H, aliph.), 1.46–1.50 (m, 2H, CH_2), 1.62 (bs, 1H, H-4′ piper.), 1.96–2.08 (dd, J = 13.2, 13.2 Hz, 2H, H-5′piper), 2.43–2.46 (m, 2H, CH_2), 2.55–2.60 (t, J = 8.6 Hz, 2H, H-2′piper.), 2.61 (bs, 1H, indan.), 2.86–2.93 (t, J = 13.6 Hz, 2H, H-6′piper.), 3.30-3.36 (t, J = 11.6 Hz, 2H, indan.), 3.41 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 6.25 (s, 1H, Ar–H), 6.36 (s, 1H, Ar–H), 7.62 (s, 1H,-CSNH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm:

12.42, 21.41, 31.88, 33.52, 35.93, 38.49, 47.28, 51.24, 54.18, 55.78, 107.89, 110.79, 131.85, 148.81, 149.52, 151.78, 186.98, 208.78.

5,6-Dimethoxy-2-{1-[butylamino(thioxo)methyl]-4-piperidyl-methyl}-1-indanone (**4l**) Yield 67%; mp 131–133°C; log *P*: 3.96; %CHN found (calculated): C 64.62 (64.59), H 7.71 (7.74), N 6.96 (6.92); IR (KBr) cm^{-1}: 3356 (N–H), 3050 (C–H), 1685 (C=O), 1067 (C=S); ^{1}H NMR δppm: 0.79–0.85 (t, $J = 10.4$ Hz, 1H, aliph.), 0.93–0.98 (t, $J = 7.2$ Hz, 3H, CH_3), 1.04–1.16 (dd, $J = 13.2$, 13.0 Hz, 2H, H-3′ piper.), 1.21–1.26 (t, $J = 9.6$ Hz, 1H, aliph.), 1.39–1.44 (m, 4H, CH_2), 1.64 (bs, 1H, H-4′ piper.), 1.97–2.08 (dd, $J = 13.2$, 13.2 Hz, 2H, H-5′piper), 2.57–2.62 (t, $J = 8.6$ Hz, 1H, H-2′piper.), 2.61 (bs, 1H, indan.), 2.85–2.92 (t, $J = 13.2$ Hz, 2H, H-6′piper.), 3.12–3.18 (t, $J = 6.8$ Hz, 2H, CH_2), 3.31–3.37 (t, $J = 11.6$ Hz, 2H, indan), 3.43 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 6.28 (s, 1H, Ar–H), 6.48 (s, 1H, Ar–H), 7.53 (s, 1H, -CSNH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δppm: 13.91, 19.89, 29.13, 78, 35.49, 36.78, 38.39, 45.91, 47.58, 54.18, 55.78, 107.64, 109.17, 131.85, 148.81, 149.52, 151.78, 184.67, 208.78.

Pharmacology

Anticonvulsant activity

The investigations were conducted on male swiss albino mice (25–30 g). Food and water were withdrawn prior to the experiments. The animals were kept under standard conditions at an ambient temperature of 25 ± 2°C and allowed free access to food and water except at the time they were brought out of the cage. All the experimental protocols were carried out with the permission from Institutional Animal Ethics committee (IAEC), form no. 416. Animals were obtained from Central Animal House Facility, Hamdard University, New Delhi-62. Registration no. and date of registration is 173/CPCSEA, 28 Jan., 2000.

Animals were randomly divided into groups of six. All the compounds (**4a**–**l**) were dissolved in polyethylene glycol. Initially, all compounds were administered ip at doses of 30, 100, and 300 mg/kg to mice. Activity was established using the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) test according to the protocol by Antiepileptic Drug Development Program (ADD), Epilepsy Branch, National Institute of Health, Bethesda, MD, USA (Kupferberg, 1989).

Maximal electroshock seizure (MES) test

Mice were prescreened 24 h before by delivering maximal electroshock 50 mA; 60 Hz and 0.2 s duration by means of corneal electrodes. A drop of 0.9% sodium chloride was instilled in each eye prior to the application of electrodes in order to prevent death of the animal. Abolition of hind limb tonic extensor component of the seizure in half or more of the animals is defined as protection. (Krall *et al.*, 1978).

Subcutaneous pentylenetetrazole test (scPTZ)

The scPTZ test utilized a dose of pentylenetetrazole 70 mg/kg. This produced clonic seizures lasting for a period of at least 5 s. The test compounds administered at the three graded doses, i.e., 30, 100, and 300 mg/kg ip. At the anticipated time the convulsant was administered subcutaneously. Animals were observed over a 30-min period. Absence of clonic spasm in half or more of the animals in the observed time period indicated a compound's ability to abolish the effect of pentylenetetrazole on seizure threshold (Clark *et al.*, 1984).

Estimation of GABA level in rat brain

As some piperidine derivatives were GABA uptake inhibitors therefore neurochemical investigation was carried out on the synthesized compounds to assess the effect on the GABA level in various regions of rat brain. Adult Wistar rats weighing 130–160 g were used in this study. The control group was treated only with the vehicle (30% v/v PEG-400). After 2 h of drug administration (100 mg/kg ip) the animal was killed by cervical dislocation and the brain regions midbrain, olfactory lob, cerebellum, and medulla oblongata were dropped into separate vials containing 4–6 ml of ice cold 80% ethanol and processed further as stated in the literature (Roberts, 1962).

Toxicity studies

Neurotoxicity (NT) The minimal motor impairment was measured in mice by the rotorod test (Yogeeswari *et al.*, 2003). The mice were trained to stay on an accelerating rotorod of diameter 3.2 cm that rotates at 10 rpm. Neurotoxicity was indicated by the inability of the animal to maintain equilibration on the rod for at least 1 min in each of the three trials. The dose at which 50% of the animals failed to balance themselves and fell off the rotating rod was determined.

Ethanol potentiation test Mice were treated with the test compound and 1 h later with ethanol 2.5 g/kg ip. This dose of ethanol did not induce lateral position in the control animals. The number of animals that were in the lateral position after receiving ethanol in each group was determined (Clerici and Pocar, 2001).

Results and discussion

Chemistry

The synthetic pathway giving access to the titled compounds (**4a–l**) is illustrated in Scheme 1. The synthesis of 5,6-dimethoxy-2-(pyridin-4-yl-methylene)indan-1-one (**1**) was involved a reaction between 5,6-dimethoxyindanone and pyridine-4-aldehyde in presence of *p*-toluenesulphonic acid. In the subsequent step, the *N*-oxide of 5,6-dimethoxy-2-(pyridin-4-yl-methylene)indan-1-one (**2**) was synthesized by treatment with hydrogen peroxide in glacial acetic acid; a usual process for *N*-oxidation, and the product was distinguished by its yellow color. On hydrogenation of the *N*-oxide of 5,6-dimethoxy-2-(pyridine-4-yl-methylene)indan-1-one **(2)**, using Pd/C, 5,6-dimethoxy-2-(piperidin-4-yl-methyl)indan-1-one (**3**) was obtained and its yield depended on the pressure of hydrogen gas passed through the reaction mixture. The optimum pressure was measured to be 10 kg/cm^2. In the last step, compound (**3**) was treated with different alkyl/aryl isothiocyanates to afford the final compounds (**4a–l**).

The sulfur atom present in the thioamide moiety of the compounds was expected to increase the lipophilicity consequently elevating drug concentration in the brain.

Pharmacology

Anticonvulsant activity

The anticonvulsant activity of all the compounds was assessed utilizing MES and scPTZ models at three graded doses 30, 100, and 300 mg/kg i.p. and the results are shown in Table 1. Most of the compounds showed significant anticonvulsant activity comparable to the standard drugs phenytoin and carbamazepine. Compounds **4d**, **4g**, and **4j** showed protection from seizures at the lowest dose in the MES screen. Compounds **4a**, **4d**, **4g**, **4j**, and **4l** were found to be most active in scPTZ screen being active at 100 mg/kg when given intraperitoneally.

Neurotoxicity

To obtain information about undesired side effects, the highly and moderately active compounds were subjected to NT (rotorod) and ethanol potentiation tests and the results are expressed in Table 2. All the compounds except **4b** and **4j** were less neurotoxic than the standard drug phenytoin. Compounds **4a**, **4d**, **4e**, and **4h** successfully passed the ethanol potentiation test.

GABA estimation

The three most active compounds **4d**, **4g**, and **4j** were subjected to the neurochemical investigation in the rat brain and the data are presented in Table 2. Results are expressed in mean ± SEM. Increase in the GABA level in rat brain suggested that the compounds act by potentiating the GABA level in brain. Significant change from control was observed with these compounds.

In the anticonvulsant screening, most of the compounds showed encouraging activity against the two seizure models. Compounds **4d**, **4g**, and **4j** were found to be highly active against MES test at a dose level 30 mg/kg at 0.5-h time interval indicative of their ability to prevent seizure spread at relatively low dose. Compounds that exhibited moderate protection against MES model at 100 mg/kg include **4a**, **4b**, **4e**, **4h**, **4k**, and **4l** at 0.5 h. Thus majority of

Table 1 Anticonvulsant and toxicity data of compounds (4a–l)

Compound	MES		scPTZ		Neurotoxicity		E-Potentiation[a]
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h	
4a	100	300	100	300	300	–	(+)
4b	100	–	300	–	100	300	(−)
4c	300	–	×	×	×	×	×
4d	30	100	100	300	300	–	(+)
4e	100	300	–	–	–	300	(+)
4f	300	–	×	×	×	×	×
4g	30	300	100	–	300	–	(−)
4h	100	300	300	300	300	–	(+)
4i	300	–	×	×	×	×	×
4j	30	100	100	300	100	300	(−)
4k	100	300	–	300	300	–	(−)
4l	100	100	100	300	300	300	(−)
Phenytoin	30	30	–	–	100	100	×
Carbamazepine	30	100	300	100	300	–	×

Number of animals in each group (n) = 6; Dose of 30, 100 and 300 mg/kg were administered ip. The figures indicate the minimum dose whereby bioactivity was demonstrated in half or more mice. The – indicates an absence of activity at maximum dose administered (300 mg/kg). The × indicates not tested

[a] Ethanol Potentiation test; The (+) indicates half or more animals passed the test while (−) indicates failed

Table 2 GABA concentration in the rat brain regions after drug administration (100 mg/kg i.p.)

Compound	GABA concentration (μg/100 mg tissue)[a]			
	Olfactory lob	Mid brain	Medulla oblongata	Cerebellum
Control	13.22 ± 0.03	44.38 ± 0.219	40.57 ± 0.21	25.27 ± 0.57
4d	15.62 ± 0.13**	61.05 ± 1.67**	49.82 ± 2.35*	31.83 ± 2.41*
4g	15.71 ± 0.06**	59.33 ± 1.89**	35.13 ± 1.18	28.06 ± 2.11
4j	13.47 ± 0.36	44.81 ± 2.41	40.75 ± 2.37	27.66 ± 1.72

[a] Statistical analysis was done by comparing the control group vs. all test groups. Each value represents the mean ± SEM of six rats; ** $P < 0.01$ and * $P < 0.05$ indicate significantly different from control. The remaining values are non-significant (ANOVA followed by Dunnetts test)

the compounds showed considerable anticonvulsant activity only at 0.5-h interval indicating that they have rapid onset and shorter duration of action.

In chemoshock investigation, those compounds that exhibited considerable activity in MES test, chosen for scPTZ study. Compounds **4a**, **4d**, **4g, 4j**, and **4l** were found to be active after 0.5 h of the drug administration at a dose of 100 mg/kg. Among these compounds **4a**, **4d**, **4j**, and **4l** continued to protect from seizures after 4.0 h at 300 mg/kg.

The structure activity relationship of these compounds was studied and found that in general all the *para*-substituted derivatives were the most active compounds of the series. The *ortho*-substituted compounds followed the activity order and the *meta*-substituted derivatives were least active. Replacing the aromatic phenyl ring with the alkyl groups did not result in any significant change in the activity. The size of the functional group had no marked effect on the activity profile.

In NT studies ethanol potentiation and rotorod tests were employed to estimate the undesired effects like sedation and ataxia produced by the compounds. Ethanol potentiation test was parallely performed along with the rotorod test to investigate the neurotoxic effects of compounds, by inducing the lateral position in the animals. Compounds **4b**, **4g**, **4j**, and **4l** showed interaction with ethanol thereby potentiating the effect of ethanol where as compounds **4a**, **4d**, **4e**, and **4h** and did not interact with ethanol. In rotorod test, compounds **4b** and **4j** were more neurotoxic than the rest of the compounds.

In our quest to understand the mechanism of anticonvulsant activity of the synthesized compounds, we selected highly active compounds (**4d**, **4g**, and **4j**) and subjected them to neurochemical investigation to estimate the 4-aminobutyric acid (GABA) levels in the different regions of rat brain. The statistical data showed (Table 2) that the concentration of GABA increased significantly in the olfactory lobe area of rat brain after administering the compounds **4d** and **4g**. Non-significant result was produced by the compound **4j**. The mid-brain region exhibited the same results as of olfactory lobe. In the medullary area and cerebellum, compound **4d** elevated the GABA concentration significantly.

The correlation of the lipophilicity (Log *P*) and in vivo anticonvulsant activity as well as NT was established and found to be non-linear. However, compound **4j** (Log $P = 5.11$) that was highly active against MES test and exhibited considerable activity against scPTZ were found to be less neurotoxic. The other highly active compounds **4d** (Log $P = 4.58$) and **4g** (Log $P = 4.58$) showed minimal neurological deficit.

Conclusion

In conclusion, the thioamide derivatives of piperidyl indanone exhibited remarkable anticonvulsant activity with lower NT. Compounds **4d** and **4g** that were most active in MES and scPTZ tests were found to elevate the GABA concentration in the rat brain significantly. Thus, the compounds may act by GABA potentiation via GABA uptake inhibitory mechanism. Such promising compounds may act as lead molecules for future investigations.

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