Med Chem Res (2016) 25:494–500
DOI 10.1007/s00044-015-1490-x

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antidepressant activity of 5-(benzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3*(*2H*)-one derivatives

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Received: 1 June 2015 / Accepted: 15 December 2015 / Published online: 20 January 2016

Abstract A new series of pyridazin-3-one derivatives were designed, synthesized and evaluated for their preclinical antidepressant effect on Swiss mice. Among the series, compounds **6c**, **6d** and **6f** exhibited significant activity profile in forced swimming test. Compounds **6c** and **6d** were most efficacious, which at dose of 50 mg kg^{-1} reduced the time of immobility by 42.85 and 38.09 %, respectively, as compared to the standard drug fluoxetine which reduced the immobility time by 45.23 % at the dose of 32 mg kg^{-1}. All the test and standard compounds were administered orally 60 min before the test. Interestingly, all active compounds did not cause any significant alteration of locomotor activity in mice as compared to control, indicating that the hybrids did not produce any motor impairment effects. The results indicate that pyridazin-*3*(*2H*)-one derivatives may have potential therapeutic value for the management of mental depression.

Keywords Pyridazin-*3*(*2H*)-one derivatives · Antidepressant activity · Forced swimming test (FST) · Locomotor activity

Abbreviations

^{1}H NMR	^{1}H nuclear magnetic resonance
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CNS	Central nervous system
DMF	Dimethylformamide
$DMSOd_6$	Deuterated dimethylsulfoxide
ESI	Electrospray ionization
FST	Forced swimming test
HCl	Chlohydric acid
IR	Infrared
KBr	Potassium bromide
LD	Lethal dose
MAOIs	Monoamine oxidase inhibitors
MDD	Major depression disorder
NaOH	Potassium hydroxide
SNRIs	Serotonin–norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants
TMS	Tetramethylsilane
TRI	Triple reuptake inhibitors
USFDA	United States Food and Drug Administration
WHO	World Health Organization

Introduction

Major depression disorder (MDD) is described as a depressive state of mind, which is associated with faulty mood, loss of interest, disruption in sleep patterns, fatigue

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and sometimes suicidal tendencies. It is a chronic and life-threatening mental illness, which remains hidden and untreated at most of the times (Hampton, 2012). World Health Organization (WHO) had estimated that 'at least 350 million people live with depression and it is the leading cause of disability worldwide' (WHO, 2012). Epidemiological studies have indicated that about 2/3 of people who commit suicide are depressed at the time of their death (Al-Habeeb *et al.*, 2013). Exact cause of depression is not clearly known, but it is believed that imbalance of neurotransmitters in brain, genetic vulnerability, stressful life events and medical problems are the main factors leading to depression (DeWeerdt, 2013). Currently available antidepressant treatments are selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAO Is), tricyclic antidepressants (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and some non-medication therapeutic options (Chancellor, 2011). Even though wide range of conventional therapies is available, nearly 15 % of depressed people are still refractory to the current existing therapies (Anderson *et al.*, 2012). In addition, most of the people suffer from relapse and experience serious side effects after treatment with current therapies (Check, 2004; Licinio and Wong, 2005). In February 2007, the USFDA displayed 'black box' label on currently available antidepressants indicating that their use may increase the risk of suicidal thinking behavior in few cases of children, adolescents and adults (Friedman and Leon, 2007). Hence, there is an urgent need to develop new class of prototypes that are more effective, tolerable and safe in depressed individuals against this deadly disorder.

Considerable interest has been paid to derivatives containing 5-arylpyridazinone moieties, because of their effects on the central nervous system (CNS) (Bosc *et al.*, 1990; Mokrosz *et al.*, 1992; Perregaard *et al.*, 1992; Sladowska, 1993). However, two pyridazine derivatives, 5-benzyl-6-methyl-2-[4-(3-trifluoromethylphenyl)piperazin-1-yl] methylpyridazin-3-one and 5-benzyl-6-methyl-2-[4-(3-chlorophenyl)piperazin-1-yl] methylpyridazin-3-one, were evaluated for their potential antidepressant effects, using classical psychopharmacological tests in mice. The intraperitoneal LD_{50} values of these compounds were, respectively, 1125.8 and 429.6 mg kg^{-1}. Both compounds (5–20 mg kg^{-1}, i.p.) reduced the duration of immobility of mice in the FST, antagonized reserpine (2.5 mg kg^{-1}, i.p.)-induced ptosis and potentiated reserpine (2.5 mg kg^{-1}, i.p.)-induced hypothermia (Rubat *et al.*, 1995).

Many reports suggest that pyridazinones and their synthetic analogues can be considered as anti-inflammatory agents (Özadali *et al.*, 2012), anticancer agents (Lattmann *et al.*, 2003) and also possess an anti-feedant activity (Huang *et al.*, 2003). On the other hand, Castro and *col.* have synthesized a series of substituted pyridazine derivatives, as new generation of triple reuptake inhibitors (TRI) and observed significant antidepressant effects (Castro *et al.*, 1994).

Based on these observations, we were interested in evaluating the pharmacological properties of a new series of 5-(benzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3*(*2H*)-one derivatives.

This report describes the chemical synthesis and biological evaluation of 5-(benzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3*(*2H*)-one derivatives as antidepressant agents.

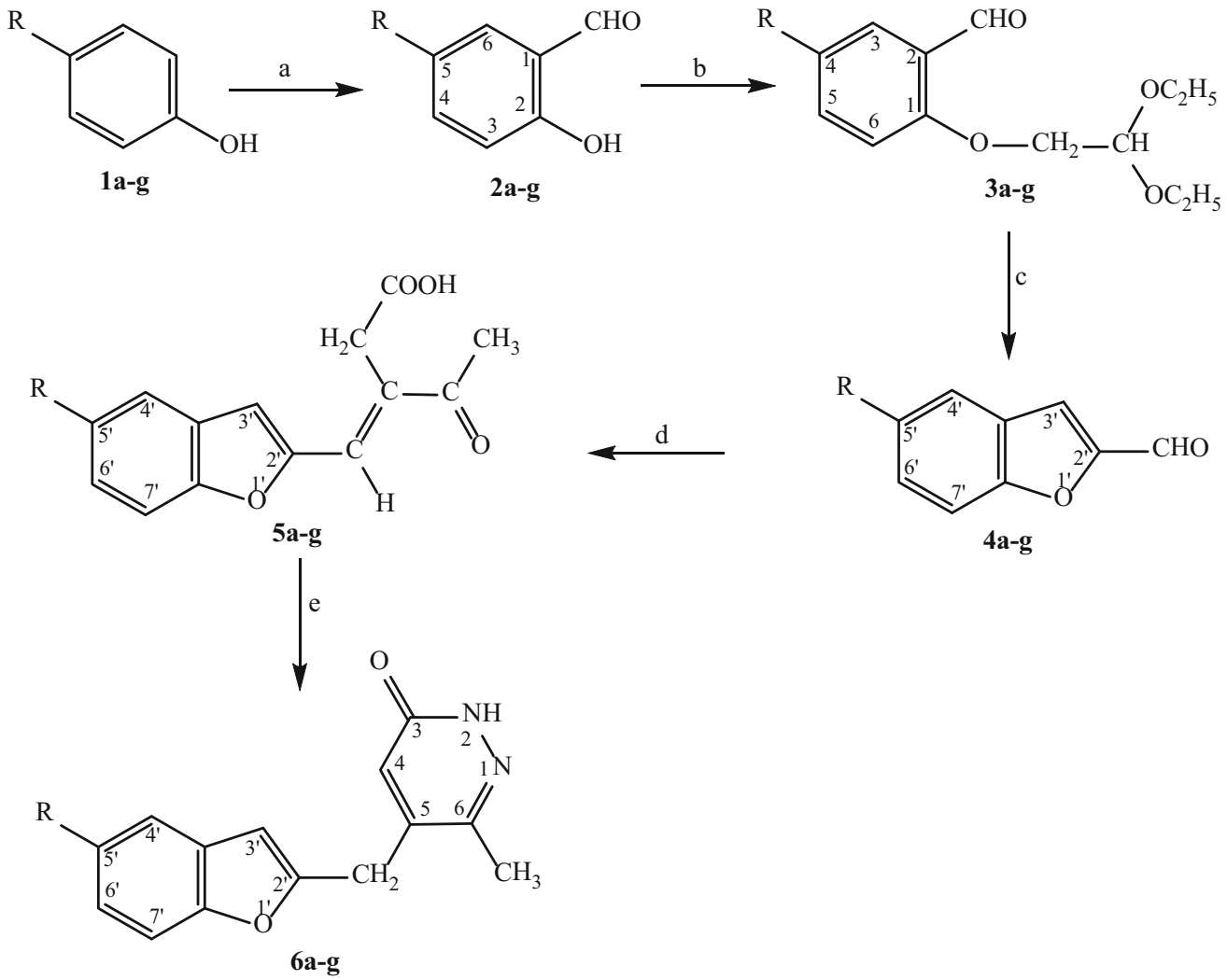
Materials and methods

Chemistry

The synthesis of 5-(benzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3*(*2H*)-one derivatives is outlined in Scheme 1. Salicylaldehydes **2a-g**, which are not commercially available, were synthesized via Reimer-Thieman (Thoer *et al.*, 1988) formylation of the appropriate substituted phenols **1** with $CHCl_3$ and NaOH. Aldehydes **2a–g** have been previously synthesized with very low yield. Briefly, reaction of intermediates **2a–g** with bromacetaldehyde diethylacetal in the presence of potassium carbonate in DMF (dimethylformamide) yielded compounds **3a–g**. These compounds **3** were cyclized to Benzo[b]furan-2-ylcarboxaldehydes **4a–g** by heating in concentrated acetic acid. Benzo[b]furanaldehydes **4** were prepared according to the methods described in the literature (Hirota *et al.*, 1986). Treatment of substituted aldehydes **4** with levulinic acid in the presence of acetic acid gave products **5a–g**, which were treated by hydrazine hydrate in ethanol at reflux temperature to afford the pyridazin-*3*(*2H*)-ones **6a–g** (Benmoussa *et al.*, 2012).

Antidepressant activity

Antidepressant activity was measured with fluoxetine as standard drug using the FST in Swiss mice. Swiss mice were placed in a vertical Plexiglas cylinder filled with water, maintained at 25 °C, for 15 min. Five to 6 min later immobility reached a plateau, where the mice remained immobile for approximately 80 % of the time. After 15 min in the water, the mice were removed and allowed to dry in a heated enclosure (32 °C) before being returned to their home cages. They were again placed in the cylinder for 24 h later, and the total duration of immobility was measured during a 5 min test (Table 1). After solubilizing the product in vegetable oil, the solution was administered directly into the stomach of mice via a technique called oral gavage (0.2 mL of solution/20 g of animals). The newly synthesized compounds were administered at a dose



Compound	R
a	H
b	CH_3
c	CH_2CH_3
d	$CH(CH_3)_2$
e	OCH_3
f	$OCH_2CH_2CH_3$
g	Cl

Scheme 1 Synthesis of target compounds **6a-g**. Reagents: *a* $CHCl_3$/NaOH 10 N, reflux 2 h; *b* $BrCH_2CH(OC_2H_5)_2/K_2CO_3$/DMF, reflux 4 h; *c* CH_3COOH, reflux 24 h; *d* $H_3CCOCH_2CH_2COOH/CH_3COOH$, reflux 24 h; *e* H_2NNH_2/EtOH, reflux 2 h

of 50 mg kg^{-1}, orally 60 min before the test. The fluoxetine was administered at a dose of 32 mg kg^{-1}, orally 60 min before the test. (Porsolt *et al.*, 1977, 1978; Petit-Demouliere *et al.*, 2005).

Results and discussion

Chemistry

Melting points were determined on a Büchi SMP 20 apparatus and are not corrected. Infrared (IR) spectra were recorded with an IR VERTEX 70 FT-IR (Bruker Optics) spectrometer. ^{1}H Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using tetramethylsilane (TMS) as internal standard and $CDCl_3$ and $DMSOd_6$ as solvent. Mass spectra were recorded on a API 3200 LC/MS/MS mass spectrometer using electrospray ionization (ESI) in positive polarity.

*General procedures for the formylation of phenols **2a–g**: Method A*

A solution of the substituted phenols **1** (0.5 mol) in 300 mL of 10 N NaOH (3 mol) was heated to 65 °C. Then 80 mL of $CHCl_3$ was added in three portions over 15 min. The mixture was heated at reflux in chloroform for 2 h. After cooling, the mixture was acidified to pH 1 with 12 N HCl, the organic layer collected and the aqueous layer extracted with chloroform. The combined chloroform solution was dried and evaporated to give a crude product which was distilled or recrystallized from an appropriate solvent.

2-Hydroxybenzaldehyde **2a**. This compound was obtained as yellowish oil, yield 20 %, bp 75–77 °C (0.4 mmHg); IR (KBr νmax cm^{-1}), 1655 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 7.00$–8.10 (m, 4H, H_3, H_4, H_5, H_6), 9.85 (s, 1H, –CHO), 10.85 (s, 1H, exch D_2O, –OH).

2-Hydroxy-5-methylbenzaldehyde **2b**. This compound was obtained as white solid, yield 95 %, mp 48–50 °C (petroleum ether); IR (KBr νmax cm^{-1}), 1650 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 2.37$ (s, 3H, $–CH_3$), 6.90 (d, 1H, $J = 8.60$ Hz, H_3), 7.25–7.50 (m, 2H, H_4, H_6), 9.80 (s, 1H, –CHO), 10.75 (s, 1H, exch D_2O, –OH).

2-Hydroxy-5-ethylbenzaldehyde **2c**. This compound was obtained as yellow oil, yield 36 %, bp 74–76 °C (0.3 mmHg); IR (KBr νmax cm^{-1}), 1651 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.25$ (t, 3H, $j = 7.41$ Hz, $–CH_2–\underline{C}H_3$), 2.70 (q, 2H, $j = 7.41$ Hz, $–\underline{C}H_2–CH_3$), 6.83 (d, 1H, $J = 9.50$ Hz, H_3), 7.26–7.52 (m, 2H, H_4, H_6), 9.87 (s, 1H, –CHO), 10.88 (s, 1H, exch D_2O, –OH).

2-Hydroxy-5-isopropylbenzaldehyde **2d**. This compound was obtained as yellow oil, yield 32 %, bp 78–80 °C (0.3 mmHg); IR (KBr νmax cm^{-1}), 1650 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.25$ (d, 6H, $j = 6.70$ Hz, $\underline{H_3}C–CH–C\underline{H_3}$), 2.95 (h, 1H, $j = 6.70$ Hz, $H_3C–C\underline{H}–CH_3$), 6.88–7.38 (m, 3H, H_3,H_4, H_6), 9.87 (s, 1H, –CHO), 10.88 (s, 1H, exch D_2O, –OH).

2-Hydroxy-5-methoxybenzaldehyde **2e**, 2-Hydroxy-5-propoxybenzaldehyde **2f** and 5-chloro-2-Hydroxybenzaldehyde **2g**, products commercially available.

*General procedures for the synthesis of 2-formylphenoxyacetadehyde diethyl acetals **3a–g**: Method B*

To a stirred suspension containing substituted 2-hydroxybenzaldehydes **2** (0.15 mol) and potassium carbonate (0.16 mol) in 100 mL of DMF, bromoacetaldehyde diethyl acetal (0.16 mol) was added drop wise. The mixture was

Table 1 Representation of percentage change in immobility duration in FST after administration of different compounds and standard drug fluoxetine to mice

Compound	Dose (mg/kg)	Immobility time ± SEM	% Immobility
Control	–	210 ± 10	100
6a	50	145 ± 25	69.04
6b	50	175 ± 20	83.33
6c	50	90 ± 25	42.85***
6d	50	80 ± 24	38.09***
6e	50	150 ± 15	71.42
6f	50	125 ± 20	59.52***
6g	50	155 ± 25	73.81
Fluoxetine	32	95 ± 10	45.23***

*** $P < 0.0001$, when compared with the control (vegetable oil)

refluxed for 4 h. After cooling, the precipitate was filtered off and the solvent evaporated under reduced pressure. The oily residue was distilled.

2-Formylphenoxy acetaldehyde diethylacetal **3a**. This compound was obtained as yellowish oil, yield 85 %, bp 181–183 °C (5 mmHg); IR 1700 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.23$ (t, 6H, $j = 6.42$ Hz, (–OCH_2–$C\underline{H}_3$)$_2$), 3.51–4.12 (m, 4H, (–$OC\underline{H}_2$–CH_3)$_2$), 4.14 (d, 2H, $j = 5.13$ Hz, –$C\underline{H}_2$–CH), 4.89 (t, 1H, $j = 5.13$ Hz, –CH_2–$C\underline{H}$), 6.95–7.82 (m, 4H, H_3, H_4, H_5, H_6), 10.48 (s, 1H, –CHO).

(2-Formyl-4-methylphenoxy)acetaldehyde diethylacetal **3b**. This compound was obtained as yellow oil, yield 80 %, bp 192–194 °C (5 mmHg); IR (KBr νmax cm^{-1}), 1700 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.25$ (t, 6H, $j = 6.40$ Hz, (–OCH_2–$C\underline{H}_3$)$_2$), 2.30 (s, 3H, –CH_3), 3.50–4.00 (m, 4H, (–$OC\underline{H}_2$–CH_3)$_2$), 4.12 (d, 2H, $j = 5.10$ Hz, –$C\underline{H}_2$–CH), 4.87 (t, 1H, $j = 5.10$ Hz, –CH_2–$C\underline{H}$), 6.90 (d, 1H, $j = 8.20$ Hz, H_6), 7.40 (dd, 1H, $j_1 = 2.11$, $j_2 = 8.20$ Hz, H_5), 7.62 (d, 1H, $j = 2.11$ Hz, H_3), 10.50 (s, 1H, –CHO).

(2-Formyl-4-ethylphenoxy)acetaldehyde diethylacetal **3c**. This compound was obtained as yellow oil, yield 81 %, bp 198–200 °C (5 mmHg); IR (KBr νmax cm^{-1}), 1690 (C=O); 2900–3000(C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.00$–1.38 (m, 9H, (–OCH_2–$C\underline{H}_3$)$_2$, –CH_2–$C\underline{H}_3$), 2.62 (q, 2H, $j = 7.61$ Hz, –$C\underline{H}_2$–CH_3), 3.50–4.00 (m, 4H, (–$OC\underline{H}_2$–CH_3)$_2$), 4.08 (d, 2H, $j = 4.70$ Hz, –$C\underline{H}_2$–CH), 4.88 (t, 1H, $j = 4.70$ Hz, –CH_2–$C\underline{H}$), 6.88 (d, 1H, $j = 8.50$ Hz, H_6), 7.57 (dd, 1H, $j_1 = 8.50$ Hz, $j_2 = 3.20$ Hz, H_5), 7.64 (d, 1H, $j = 3.20$ Hz, H_3), 10.50 (s, 1H, –CHO).

(2-Formyl-4-isopropylphenoxy)acetaldehyde diethylacetal **3d**. This compound was obtained as yellow oil, yield 80 %, bp 160–162 °C (0.3 mmHg); IR (KBr νmax cm^{-1}), 1700 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.00$–1.30 (m, 12H, (–OCH_2–$C\underline{H}_3$)$_2$, $\underline{H}_3$C–CH–$C\underline{H}_3$), 2.92 (h, 1H, $j = 6.41$ Hz, H_3C–$C\underline{H}$–CH_3), 3.50–3.90 (m, 4H, (–$OC\underline{H}_2$–CH_3)$_2$), 4.10 (d, 2H, $j = 5.30$ Hz, –$C\underline{H}_2$–CH), 4.88 (t, 1H, $j = 5.30$ Hz, –CH_2–$C\underline{H}$), 6.90 (d, 1H, $j = 8.51$ Hz, H_6), 7.40 (dd, 1H, $j_1 = 2.70$, $j_2 = 8.50$ Hz, H_5), 7.70 (d, 1H, $j = 2.70$ Hz, H_3), 10.50 (s, 1H, –CHO).

(2-Formyl-4-methoxyphenoxy)acetaldehyde diethylacetal **3e**. This compound was obtained as yellow oil, yield 68 %, bp 154–156 °C (0.3 mmHg); IR (KBr νmax cm^{-1}), 1700 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.25$ (t, 6H, $j = 6.40$ Hz, (–OCH_2–$C\underline{H}_3$)$_2$), 2.38 (s, 3H, –OCH_3), 3.45–4.30 (m, 4H, (–$OC\underline{H}_2$–CH_3)$_2$), 4.42 (d, 2H, $j = 5.10$ Hz, –$C\underline{H}_2$–CH), 4.97 (t, 1H, $j = 5.10$ Hz, –CH_2–$C\underline{H}$), 6.95 (d, 1H, $j = 8.21$ Hz, H_6), 7.45 (dd, 1H, $j_1 = 2.11$, $j_2 = 8.21$ Hz, H_5), 7.65 (d, 1H, $j = 2.11$ Hz, H_3), 10.56 (s, 1H, –CHO).

(2-Formyl-4-propoxyphenoxy)acetaldehyde diethylacetal **3f**. This compound was obtained as yellow oil, yield 67 %, bp 180–183 °C (0.5 mmHg); IR (KBr νmax cm^{-1}), 1700 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.01$ (t, 3H, $j = 7.21$ Hz, –OCH_2–CH_2–$C\underline{H}_3$), 1.24 (t, 6H, $j = 6.91$ Hz, (–OCH_2–$C\underline{H}_3$)$_2$), 1.78 (m, 2H, –OCH_2–$C\underline{H}_2$–CH_3), 3.69 (m, 4H, (–$OC\underline{H}_2$–CH_3)$_2$), 3.90 (t, 2H, $j = 6.21$ Hz, –$OC\underline{H}_2$–CH_2–CH_3), 4.07 (d, 2H, $j = 5.11$ Hz, –$C\underline{H}_2$–CH), 4.83 (t, 1H, $j = 5.11$ Hz, –CH_2–$C\underline{H}$), 6.76–7.31 (m, 3H, H_3, H_5, H_6), 10.46 (s, 1H, –CHO).

(4-Chloro-2-formylphenoxy)acetaldehyde diethylacetal **3g**. This compound was obtained as yellow oil, yield 90 %, bp 140–143 °C (0.3 mmHg); IR (KBr νmax cm^{-1}), 1690 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.26$ (t, 6H, $j = 7.60$ Hz, (–OCH_2–$C\underline{H}_3$)$_2$), 3.50–4.00 (m, 4H, (–$OC\underline{H}_2$–CH_3)$_2$), 4.10 (d, 2H, $j = 5.71$ Hz, –$C\underline{H}_2$–CH), 4.87 (t, 1H, $j = 5.71$ Hz, –CH_2–$C\underline{H}$), 6.95 (d, 1H, $j = 8.50$ Hz, H_6), 7.48 (dd, 1H, $j_1 = 2.81$, $j_2 = 8.50$ Hz, H_5), 7.79 (d, 1H, $j = 2.81$ Hz, H_3), 10.43 (s, 1H, –CHO).

*General procedures for the synthesis of substituted Benzo[b]furan-2-yl carboxaldehydes **4a**–**g**: Method C*

A stirred solution of compounds **3** (0.1 mol) in 35 mL of concentrated acetic acid was refluxed for 24 h. After cooling, the solution was evaporated to dryness. The crude product was distilled or recrystallized from an appropriate solvent.

2-Formylbenzo[b]furan **4a**. This compound was obtained as yellow oil, yield 75 %, bp 121–123 °C (3 mmHg); IR (KBr νmax cm^{-1}), 1680 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 7.26$–7.74 (m, 5H, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$, $H_{7'}$), 9.84 (s, 1H, –CHO).

2-Formyl-5-methylbenzo[b]furan **4b**. This compound was obtained as yellow solid, yield 66 %, mp 26–27 °C (ehanol/water 9/1); IR (KBr νmax cm^{-1}), 1680 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 2.38$ (s, 3H, –CH_3), 7.40–7.77 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{6'}$,$H_{7'}$), 9.87 (s, 1H, –CHO).

5-Ethyl-2-formylbenzo[b]furan **4c**. This compound was obtained as yellowish oil, yield 80 %, bp 130–132 °C (3 mmHg); IR (KBr νmax cm^{-1}), 1680 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.30$ (t, 3H, $j = 7.90$ Hz, –CH_2–$C\underline{H}_3$), 2.76 (q, 2H, $j = 7.90$ Hz, –$C\underline{H}_2$–CH_3), 7.25–7.70 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{6'}$, $H_{7'}$), 9.86 (s, 1H, –CHO).

2-Formyl-5-isopropylbenzo[b]furan **4d**. This compound was obtained as yellowish oil, yield 56 %, bp 131–133 °C (3 mmHg); IR (KBr νmax cm^{-1}), 1700 (C=O), 2900–3000 (C–H); ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta = 1.28$ (d, 6H, $j = 6.30$ Hz, $\underline{H}_3$C–CH–$C\underline{H}_3$), 3.00 (h, 1H, $j = 6.30$ Hz, H_3C–$C\underline{H}$–CH_3), 7.48–7.63 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{6'}$, $H_{7'}$), 9.85 (s, 1H, –CHO).

2-Formyl-5-methoxybenzo[b]furan **4e**. This compound was obtained as yellow solid, yield 70 %, mp 82–84 (diisopropyl ether); IR (KBr νmax cm^{-1}), 1700 (C=O), 2900–3000 (C–H); ^1H NMR ($CDCl_3$, 400 MHz), $\delta = 2.41$ (s, 3H, $–OCH_3$), 7.43–7.80 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{6'}$, $H_{7'}$), 9.89 (s, 1H, –CHO).

2-Formyl-5-propoxybenzo[b]furan **4f**. This compound was obtained as yellow solid, yield 85 %, mp 65–67 °C (diisopropyl ether); IR (KBr νmax cm^{-1}), 1700 (C=O), 2900–3000 (C–H); ^1H NMR ($CDCl_3$, 400 MHz), $\delta = 0.97$ (t, 3H, $j = 7.20$ Hz, $–OCH_2–CH_2–C\underline{H}_3$), 1.73 (m, 2H, $–OCH_2–C\underline{H}_2–CH_3$), 3.94 (t, 2H, $j = 6.60$, $–OC\underline{H}_2–CH_2–CH_3$), 7.15 (dd, 1H, $j_1 = 9.10$ Hz, $j_2 = 2.70$ Hz, $H_{6'}$), 7.31 (d, 1H, $j = 2.70$ Hz, $H_{4'}$), 7.61 (d, 1H, $j = 9.10$ Hz, $H_{7'}$), 7.86 (s, 1H, $H_{3'}$), 9.79 (s, 1H, –CHO).

5-Chloro-2-formylbenzo[b]furan **4g**. This compound was obtained as yellow solid, yield 60 %, mp 126–127 °C (ethyl acetate); IR (KBr νmax cm^{-1}), 1670 (C=O); ^1H NMR ($CDCl_3$, 400 MHz), $\delta = 7.25–7.75$ (m, 4H, $H_{3'}$, $H_{4'}$, $H_{6'}$, $H_{7'}$), 9.86 (s, 1H, CHO).

*General procedures for the synthesis of substituted 3-benzo[b]furan-2-ylmethylene-levulinic acids **5a–g**: Method D*

A stirred solution of compounds **4** (0.1 mol) in 35 mL of concentrated acetic acid was refluxed for 24 h. After cooling, the solution was evaporated to dryness. The obtained residue was used crude for the continuation.

*General procedures for the synthesis of substituted 5-(benzo[b]furan-2-ylmethyl)-6-methylpyridazin-3(2H)-ones **6a–g**: Method E*

The mixture of acids **5** and hydrazine hydrate solution in ethanol was refluxed for 2 h; the precipitate formed is filtered and recrystallized from an appropriate solvent.

5-(Benzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3(2H)*-one **6a**. This compound was obtained as yellow solid, yield 69 %, mp 181–183 °C (ethanol); IR (KBr νmax cm^{-1}), 1604 (C=N), 1662 (C=O), 2900–3000 (C–H); ^1H NMR ($DMSOd_6$, 400 MHz), $\delta = 2.22$ (s, 3H, $–N=C–CH_3$), 4.08 (s, 2H, $–CH_2–$), 6.97 (s, 1H, H_4), 6.71 (s, 1H, $H_{3'}$), 7.19–7.58 (m, 4H, $H_{4'}$, $H_{5'}$, $H_{6'}$, $H_{7'}$), 12.71 (ls, 1H, NH). MS m/z; 241.2 $[M + H]^+$, 238.9 $[M + H]^-$, 263.3 $[M + Na]^+$.

5-(5-Methylbenzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3(2H)*-one **6b**. This compound was obtained as yellow solid, yield 80 %, mp 183–184 °C (ethanol); IR (KBr νmax cm^{-1}), 1603 (C=N), 1666 (C=O), 2900–3000 (C–H); ^1H NMR ($DMSOd_6$, 400 MHz), $\delta = 2.23$ (s, 3H, $–N=C–CH_3$), 2.37 (s, 3H, $Ar–CH_3$), 4.07 (s, 2H, $–CH_2–$), 6.58 (s, 1H, H_4), 6.64 (s, 1H, $H_{3'}$), 7.07 (dd, 1H, $j_1 = 8.41$ Hz, $j_2 = 1.21$ Hz, $H_{6'}$), 7.36 (d, 1H, $j = 1.21$ Hz, $H_{4'}$), 7.40 (d, 1H, $j = 8.41$ Hz, $H_{7'}$), 12.74 (ls, 1H, NH). MS m/z; 255.1 $[M + H]^+$, 253.3 $[M + H]^-$, 276.9 $[M + Na]^+$.

5-(5-Ethylbenzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3(2H)*-one **6c**. This compound was obtained as brown solid, yield 73 %, mp 180–181 °C (ethanol); IR (KBr νmax cm^{-1}), 1605 (C=N), 1661 (C=O), 2900–3000 (C–H); ^1H NMR ($DMSOd_6$, 400 MHz), $\delta = 1.18$ (t, 3H, $j = 7.50$ Hz, $–CH_2–C\underline{H}_3$), 2.21 (s, 3H, $–N=C–CH_3$), 2.65 (q, 2H, $j = 7.50$ Hz, $–C\underline{H}_2–CH_3$), 4.05 (s, 2H, $–CH_2–$), 6.56 (s, 1H, H_4), 6.64 (s, 1H, $H_{3'}$), 7.08 (dd, 1H, $j_1 = 8.40$ Hz, $j_2 = 1.80$ Hz, $H_{6'}$), 7.37 (d, 1H, $j = 1.80$ Hz, $H_{4'}$), 7.41 (d, 1H, $j = 8.40$ Hz, $H_{7'}$), 12.76 (ls, 1H, NH). MS m/z; 269.5 $[M + H]^+$, 267.1 $[M + H]^-$, 291.3 $[M + Na]^+$.

5-(5-Isopropylbenzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3(2H)*-one **6d**. This compound was obtained as brown solid, yield 82 %, mp 185–186 °C (ethanol); IR (KBr νmax cm^{-1}), 1605 (C=N), 1682 (C=O), 2900–3000 (C–H); ^1H NMR ($DMSOd_6$, 400 MHz), $\delta = 1.24$ (d, 6H, $j = 6.90$ Hz, $\underline{H}_3C–CH–C\underline{H}_3$), 2.10 (s, 3H, $–N=C–CH_3$), 2.99 (h, 1H, $j = 6.90$ Hz, $H_3C–C\underline{H}–CH_3$), 3.90 (s, 2H, $–CH_2–$), 7.30–7.76 (m, 5H, H_4, $H_{3'}$, $H_{4'}$, $H_{6'}$, $H_{7'}$), 12.32 (ls, 1H, NH). MS m/z; 283.4 $[M + H]^+$, 281.2 $[M + H]^-$, 337.4 $[M + Na]^+$.

5-(5-Methoxybenzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3(2H)*-one **6e**. This compound was obtained as yellow solid, yield 78 %, mp 190–192 °C (ethanol); IR (KBr νmax cm^{-1}), 1650 (C=O), 2950–3000 (C–H); ^1H NMR ($DMSOd_6$, 400 MHz), $\delta = 2.25$ (s, 3H, $–N=C–CH_3$), 3.74 (s, 3H, $–OCH_3$), 4.04 (s, 2H, $–CH_2–$), 6.55 (s, 1H, H_4), 6.64 (s, 1H, $H_{3'}$), 6.82 (dd, 1H, $j = 8.70$ and 2.71 Hz, $H_{6'}$), 7.08 (d, 1H, $j = 2.71$ Hz, $H_{4'}$), 7.40 (d, 1H, $j = 8.70$ Hz, $H_{7'}$), 12.75 (ls, 1H, NH). MS m/z; 299.4 $[M + H]^+$, 297.1 $[M + H]^-$, 321.4 $[M + Na]^+$.

5-(5-Propoxybenzo[b]furan-2-ylmethyl)-6-methylpyridazin-*3(2H)*-one **6f**. This compound was obtained as brown solid, yield 87 %, mp 194–196 °C (ethanol); IR (KBr νmax cm^{-1}), 1652(C=O), 2940–3000(C–H); ^1H NMR ($DMSOd_6$, 400 MHz), $\delta = 0.96$ (t, 3H, $j = 6.90$ Hz, $–OCH_2–CH_2–C\underline{H}_3$), 1.71 (m, 2H, $–OCH_2–C\underline{H}_2–CH_3$), 2.21 (s, 3H, $–N=C–CH_3$), 3.90 (t, 2H, $j = 6.90$ Hz, $–OC\underline{H}_2–CH_2–CH_3$), 4.04 (s, 2H, $–CH_2–$), 6.55 (s, 1H, H_4), 6.62 (s, 1H, $H_{3'}$), 6.81 (dd, 1H, $j = 9.00$ and 2.71 Hz, $H_{6'}$), 7.06 (d, 1H, $j = 2.71$ Hz, $H_{4'}$), 7.38 (d, 1H, $j = 9.00$ Hz, $H_{7'}$), 12.74 (ls, 1H, NH).

5-[(5-Chlorobenzo[b]furan-2-yl)methyl]-6-methylpyridazin-*3(2H)*-one **6g**. This compound was obtained as yellow solid, yield 70 %, mp 198–200 °C (ethanol); IR (KBr νmax cm^{-1}), 1649(C=O); ^1H NMR ($DMSOd_6$, 400 MHz), $\delta = 2.23$ (s, 3H, $–N=C–CH_3$), 4.11 (s, 2H, $–CH_2–$), 6.60 (s, 1H, H_4), 6.74 (s, 1H, $H_{3'}$), 7.29 (dd, 1H, $j = 8.71$ and 2.16 Hz, $H_{6'}$), 7.58 (d, 1H, $j = 8.71$ Hz, $H_{4'}$), 7.66 (d, 1H,

$j = 2.16$ Hz, $H_{7'}$), 12.76 (ls, 1H, NH). MS m/z; 275.0 $[M + H]^+$, 272.7 $[M + H]^-$, 297.0 $[M + Na]^+$.

Antidepressant activity

To evaluate the structure–activity relationship, the effects of the substituents on C5 of the benzofuran ring were considered. As shown in Table 1, we noticed that the increase in the aliphatic chain size in the C5 of benzofuran reduced the immobility time of the mice. Among all the pyridazinone compounds tested at a dose of 50 mg kg^{-1} orally in adult mice in FST (Hirota *et al.*, 1986), compounds **6c** and **6d** were found to be the most active structures, compared to fluoxetine tested at a dose of 32 mg kg^{-1}.

In conclusion, through our drug design and discovery program, we were able to develop a new series of pyridazinone derivatives as potential antidepressant agents. Our ongoing studies are directed toward the detailed mechanistic and pharmacokinetic studies on compound **6d** so as to advance this molecule into a therapeutic option. Interestingly, all active compounds did not cause any significant alteration of locomotor activity in mice as compared to control, indicating that the hybrids did not produce any motor impairment effects. The results indicate that pyridazin-*3*(*2H*)-one derivatives may have potential therapeutic value for the management of mental depression.

Acknowledgments The authors are grateful to the University Mohammed V and Laboratory of control of drugs, Rabat-Morocco, for, IR, RMN and MASS spectra and the studies of antidepressant activity.

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