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Original article

Synthesis and evaluation of hexahydropyrrolo[3,4-*d*]isoxazole-4,6-diones as anti-stress agents

Rahul Badru, Preet Anand, Baldev Singh*

Department of Chemistry, Punjabi University, Patiala 147002, India

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ABSTRACT

A series of 2,3-diphenyl-5-(naphthalen-1-yl)-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione derivatives were synthesized via 1,3-dipolar cycloaddition of azomethine *N*-oxides with *N*-(α-naphthyl)maleimide. The pyrrolo-isoxazole derivatives were assigned cis- and trans- configurations (3-A and 3-B) with respect to proton C_3-H on azomethinic carbon on the basis of their ^{1}H NMR. The reaction proceeds through cis- endo addition rule indicating the predominance of cis isomer. The cis- and trans-isomers of a prototype compound **3a** *i.e.,* compound **3a-A** and compound **3a-B** were evaluated for anti-stress activity in immobilization-induced acute stress. Compound **3a-A** (5 and 10 mg/kg) and compound **3a-B** (10 mg/kg) attenuated immobilization stress-induced behavioral alterations in Swiss albino mice suggesting that pyrrolo-isoxazole may serve as lead molecule for the development of anti-stress agents.

1. Introduction

Stress has been described as a sum total of all the reactions of the body that disturb the normal physiological equilibrium and result in a state of threatened homeostasis. Exposure to stress stimuli induces various changes in the body including alteration in behavior, autonomic function, hyper-activation of hypothalamus-pituitary adrenal (HPA) axis and thus, secretion of hormones including adrenocorticotropin hormone (ACTH) and corticosterone [1]. Stress-induced hyper-activation of HPA axis leads to various diseases such as hypertension [2], immunosuppression [3], reproductive dysfunction [4], mental depression, schizophrenia, amnesia and neurodegeneration [5]. Currently, the effective drugs are not available in modern medicine to counter stress and associated behavioral changes and therefore, the identification of new effective anti-stress agents is required for effective stress management.

Previous studies revealed that isoxazoline moieties possess varied biological activities like anti cancer [6], anti-tubercular [7], tyrosine phosphatase inhibitory activity [8], antifungal [9], anti-influenza virus [10], glycoprotein IIb/IIIa receptor antagonists [11], analgesic and anti-inflammatory [12], β-adrenergic receptor antagonist properties [13], anti-HIV [14], anti-convulsant [15]. The prominent role of tyrosine hydroxylase enzyme has been postulated in stress models as the studies have shown its increased expression in different brain and adrenal tissue following stressful conditions [16]. Furthermore, the drugs showing tyrosine hydroxylase inhibitory activity has been reported to exhibit potent anti-stress effects in different models [17]. The studies have shown that pyrrolo-isoxazoles possess the tyrosine hydroxylase inhibitory activity [18]. An increased activity of tyrosine hydroxylase leads to increase in norepinephrine release which is responsible for stress related behavioral alterations. It has been shown that pyrrolo-isoxazole carboxylic acid derivatives decrease catecholamine and 5-HT levels in brain [19]. Furthermore, structurally related isoxazoline derivatives have also been reported to exhibit anti-stress effects in an acute model of immobilization stress in rats [20]. Based on these it is hypothesized that pyrrolo-isoxazole derivatives may be potentially exploited for anti-stress activity. Therefore, the present study was designed to synthesize series of new pyrrolo-isoxazole derivatives and evaluate one of the prototype chemical moieties (cis- and trans- isomers) for anti-stress activity in immobilization model.

2. Chemistry

With viable reaction conditions and under inert nitrogen atmosphere, 1,3-dipolar cycloaddition reaction between several different substituted nitrones [21] and *N*-(α-naphthyl)maleimide

* Corresponding author. Tel.: +91 9988302741 (mobile).
E-mail address: drbaldev.chem@gmail.com (B. Singh).

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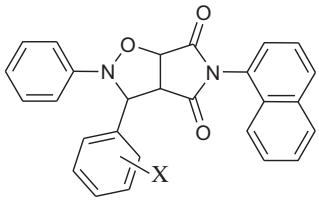
Table 1
Synthesis of dihydro-5-(naphthalen-1-yl)-2,3-diphenyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione derivatives.



Compound - 3

Compound	X	% Yield	A:B	Melting point in °C	
				A	B
3a	H	74	53:47	205–206	198–199
3b	2-CH_3	82	62:38	220–222	205–206
3c	3-CH_3	88	60:40	222–223	202–204
3d	4-CH_3	78	64:36	215–217	206–207
3e	2-Cl	84	62:38	189–191	180–182
3f	3-Cl	92	60:40	192–193	185–186
3g	4-Cl	88	63:37	222–223	210–212
3h	2-OH	86	64:36	232–233	205–206
3i	3-OH	82	58:42	197–199	192–193
3j	4-OH	88	53:47	210–212	197–199
3k	2-OCH_3	78	58:42	202–204	188–190
3l	3-OCH_3	84	62:38	208–210	186–187
3m	4-OCH_3	85	58:42	198–199	192–194
3n	2-NO_2	80	64:36	206–207	184–185
3o	3-NO_2	78	58:42	215–216	202–203
3p	4-NO_2	72	60:40	238–240	220–222

has been examined and found to be independent of the nature of substituents as is evident from their relative yields (Table 1**)** with electron-rich (entry **3b**, **3c**, **3d**, **3h**, **3i**, **3j**, **3k**, **3l** and **3m**), electron-neutral (entry **3a**), electron-poor (entries **3e**, **3f**, **3g**, **3n**, **3o** and **3p**), *o*-substituted (entries **3b**, **3e**, **3h**, **3k** and **3n**), *m*-substituted (entries **3c**, **3f**, **3i**, **3l and 3o**) and *p*-substituted (entries **3d**, **3g**, **3j**, **3m** and **3p**) benzaldehyde substrates.

The starting compounds, azomethine *N*-oxides 1 (Scheme 1) and *N*-(α-naphthyl) maleimide 2 (Scheme-2) were synthesized by following similar procedure as reported in literature [22,23]. The compound **1** reacted with compound **2** in sodium dried toluene under refluxing conditions to afford a mixture of diastereoisomers, which were separated and were characterized as cis and trans 4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6–dione derivatives **3a**–**p** (Scheme 3).

A 1,3-dipolar cycloaddition reaction between azomethine *N*-oxide 1 and maleimide 2 seems to occur from the less hindered face of the double bond of malemide ring to afford a mixture of stereoisomers 3-A and 3-B [24] as indicated by TLC and ^{1}H NMR analysis, which were separated by flash column chromatography. The two diastereomers were isolated in approximately 3:2 ratio.

In their I.R. spectra these derivatives exhibit a strong absorption band (ν_{max}) in the range 1703–1725 cm^{-1} and a shoulder band in the range 1781–1787 cm^{-1} due to imide carbonyl groups. In the ^{1}H NMR spectrum of trans diastereomer C_3-H and C_{6a}-H were obtained as doublets at δ 5.5–5.6 and 5.0–5.1 with $J \approx$ 7.88–8.04 Hz and 8.92–9.12 Hz respectively on coupling with proton C_{3a}-H, while proton C_{3a}-H was obtained at δ 4.3 as double doublet with $J \approx$ 8.24–8.88 Hz and 8.12–8.28 Hz on coupling with protons C_3-H and C_{6a}-H respectively **(3-B)**. However in the ^{1}H NMR spectra of cis diastereomer C_3-H and C_{6a}-H were obtained as doublets at δ 5.3–5.4 and 5.0 with $J \approx$ 7.88–7.96 Hz and 8.40–8.48 Hz respectively on coupling with proton C_{3a}-H, while proton signal for C_{3a}-H was obtained at δ 4.3 as double doublet with $J \approx$ 8.28–8.92 Hz and 8.10–8.18 Hz on coupling with protons C_3-H and C_{6a}-H respectively (**3-A**). In all the reactions studied the cis and trans isomers were obtained nearly in 3:2 ratio indicating the predominance of endo-type transition state over the exo-type [24].

3. Pharmacology

One of the pyrrolo-isoxazole derivatives *i.e.*, compound **3a** was considered as a prototype and its two isomers (cis- and trans-) in three different doses 2 mg/kg, 5 mg/kg and 10 mg/kg were evaluated for potential anti-stress activity in Swiss albino mice. Diazepam (2 mg/kg) was employed as a standard anti-stress agent. Mice were subjected to acute immobilization stress and resulting behavioral alterations were evaluated using actophotometer, social interaction and open field tests.

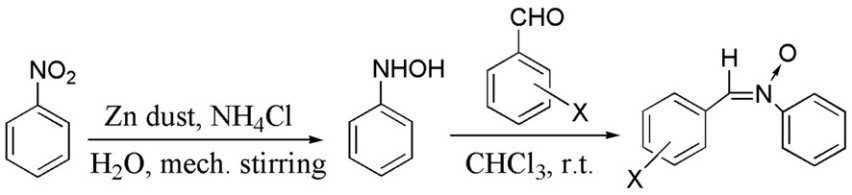
4. Results and discussion

4.1. Biological activity

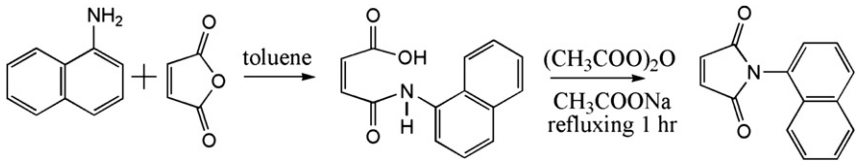
4.1.1. Effect of compound *3a-A* and compound *3a-B* on head dips and rearings in the hole-board test in immobilization subjected mice

The head dips are considered as an index of curiosity or exploration; while the frequency of rearing reflects the exploration of novel surroundings. In immobilization subjected mice, the frequency of head dips and rearing was decreased significantly as compared to the normal control group. Treatment with the compound **3a-A** (5 and 10 mg/kg *i.p.*) and diazepam (2 mg/kg *i.p.*) significantly attenuated immobilization stress-induced decrease in the frequency of head dips and rearing. However, treatment of the compound **3a-A** at lower concentrations (2 mg/kg *i.p.*) did not modulate stress-induced changes in the frequency of head dips and rearing in a significant manner.

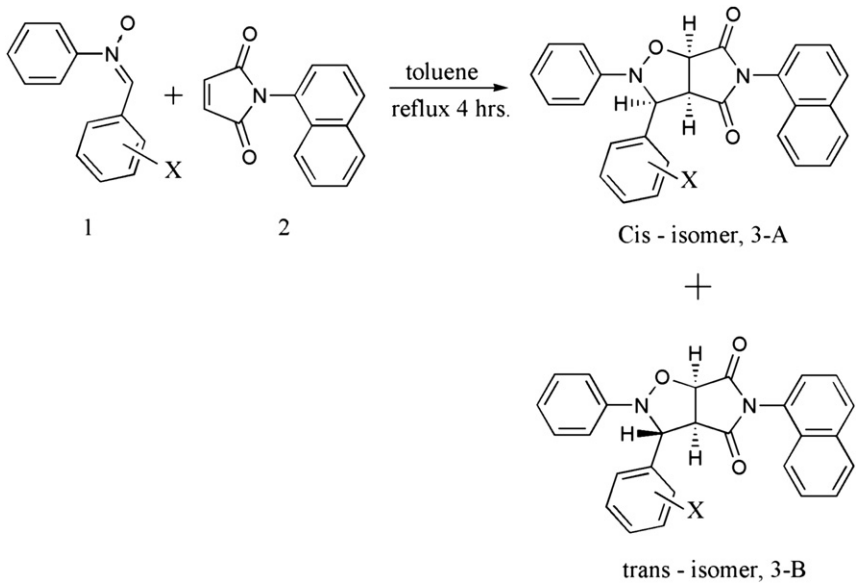
Treatment with the compound **3a-B** (10 mg/kg *i.p.*) attenuated stress-induced decrease in the frequency of head dips and rearing. However, the comparative effect of trans- isomer on restoration of head dips and rearing was significantly less as compared to corresponding cis- isomer at the same dose level of 10 mg/kg. Treatment with compound **3a-B** (2 and 5 mg/kg *i.p.*) did not modulate immobilization stress-induced decrease in the frequency of head dips and rearing (Figs. 1 and 2)**.** Furthermore, *per se* treatment with compound **3a-A** (10 mg/kg *i.p.*) and compound **3a-B** (10 mg/kg *i.p.*) did not modulate the frequency of head dips and rearing in the normal mice.



Scheme 1. Synthesis of azomethine *N*-oxides.



Scheme 2. Synthesis of *N*-(α-naphthyl)maleimide.



Scheme 3. Cycloaddition of azomethine *N*-oxide and *N*-(α-naphthyl)maleimide leading to the synthesis of diastereoisomers.

*4.1.2. Effect of compound **3a-A** and compound **3a-B** on line crossing and rearing in open field test in immobilization subjected mice*

The line crossings are taken as an indicative of motor activity and the frequency of rearing reflects the exploration of novel surroundings. Immobilization stress for 120 min decreased the number of line crossings and frequency of rearing as compared to the normal control group. Treatment with the compound **3a-A** (5 and 10 mg/kg) and diazepam (2 mg/kg *i.p.*) attenuated immobilization stress-induced decrease in the number of line crossings and frequency of rearing in a significant manner.

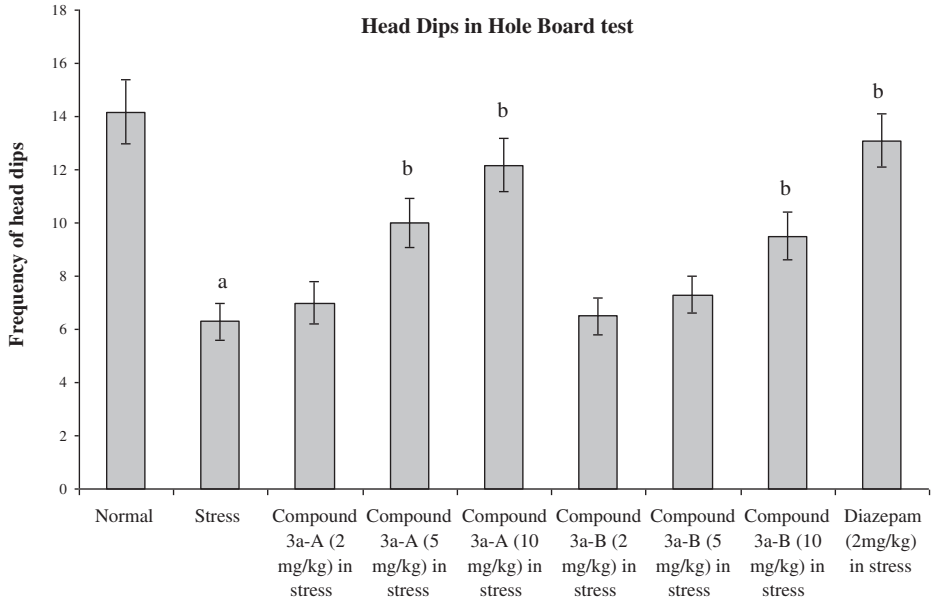


Fig. 1. Assessment of the exploratory behavior of animals in terms of number of head dips in 10 min time interval in the hole board test for investigating the anti-stress effects of different doses of compounds **3a-A** and **3a-B**. Results are represented as mean ± S.E.M. With $n = 10$ in each group.[a] $p < 0.05$ as compared to the normal control;[b] $p < 0.05$ as compared to the stress control.

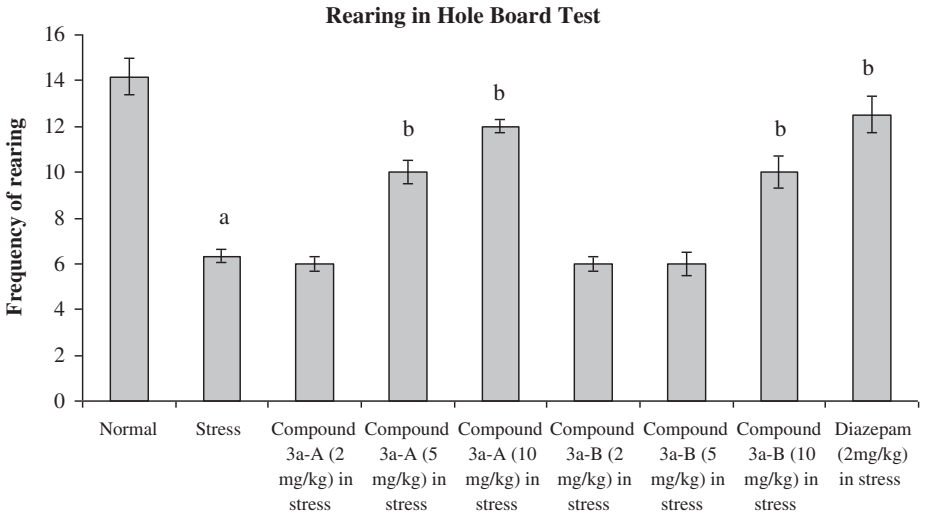


Fig. 2. Assessment of the exploratory behavior of animals in terms of frequency of rearing in 10 min time interval in the hole board test for investigating the anti-stress effects of different doses of compounds **3a-A** and **3a-B**. Results are represented as mean ± S.E.M. With $n = 10$ in each group.[a] $p < 0.05$ as compared to the normal control;[b] $p < 0.05$ as compared to the stress control.

Treatment with the compound **3a-B** (10 mg/kg *i.p.*) attenuated stress-induced decrease in the number of line crossings and frequency of rearing. However, the restorative effects of trans-isomer on line crossings and frequency of rearing was significantly less as compared to corresponding cis- isomer at the same dose level of 10 mg/kg. Treatment with compound **3a-B** (2 and 5 mg/kg *i.p.*) failed to attenuate immobilization stress-induced decrease in the number of line crossings and frequency of rearing (Figs. 3 and 4).

*4.1.3. Effect of compound **3a-A** and compound **3a-B** on following and avoidance in the social interaction test in immobilization subjected mice*

In immobilization subjected mice, the non-social behavior (avoiding the partner) was more predominant as compared to the normal control group, which exhibited social behavior (following the partner). Treatment with the compound **3a-A** (5 and 10 mg/kg) and diazepam (2 mg/kg *i.p.*) significantly attenuated immobilization stress-induced non-social behavior. Treatment with the compound **3a-B** (10 mg/kg *i.p.*) attenuated stress-induced increase in non-social behavior. However, the comparative effect of trans-isomer on restoration of social behavior was significantly less as compared to corresponding cis- isomer at the same dose level of 10 mg/kg. Treatment with compound **3a-B** (2 and 5 mg/kg *i.p.*) failed to attenuate immobilization stress-induced increase in non-social behavior (Table 2).

*4.1.4. Effect of compound **3a-A** and compound **3a-B** on the locomotor activity in actophotometer test in immobilization stress subjected mice*

Single exposure of immobilization stress of 120 min led to significant decrease in the locomotor activity in actophotometer

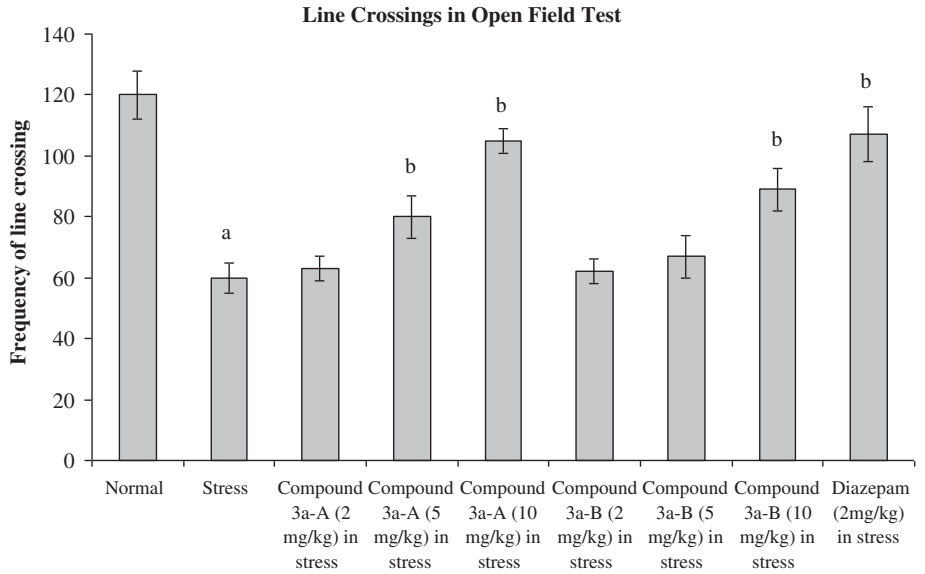


Fig. 3. Assessment of spontaneous, exploratory and ambulatory activity in terms of the line crossings in 10 min time interval in the open field test for investigating the anti-stress effects of different doses of compounds **3a-A** and **3a-B**. Results are represented as mean ± S.E.M. With $n = 10$ in each group.[a] $p < 0.05$ as compared to the normal control;[b] $p < 0.05$ as compared to the stress control.

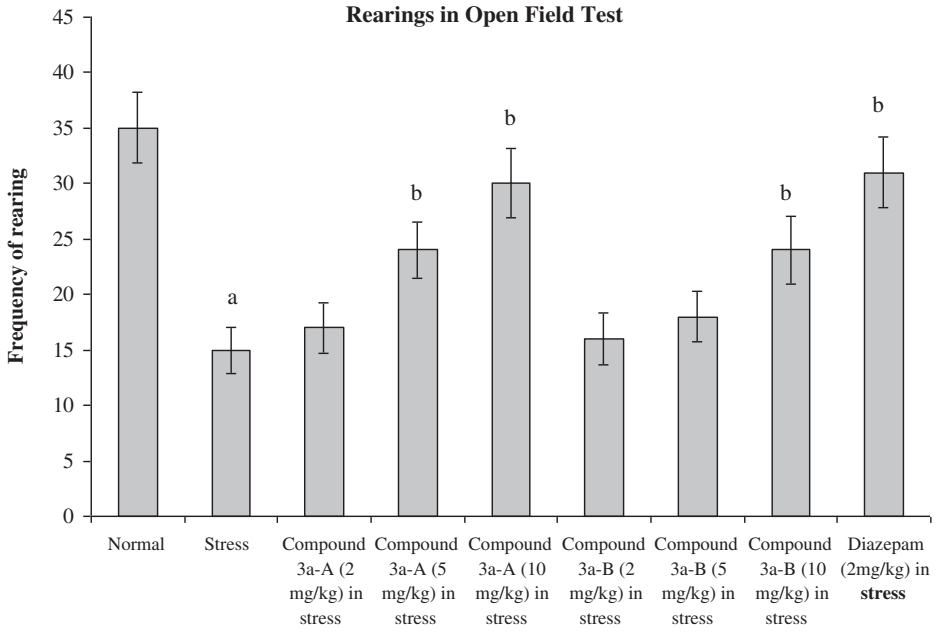


Fig. 4. Assessment of spontaneous, exploratory and ambulatory activity in terms of the frequency of rearing in 10 min time interval in the open field test for investigating the anti-stress effect of different doses of compounds **3a-A** and **3a-B**. Results are represented as mean ± S.E.M. With $n = 10$ in each group.[a] $p < 0.05$ as compared to the normal control;[b] $p < 0.05$ as compared to the stress control.

test. Administration of compound **3a-A** (5 and 10 mg/kg *i.p.*) and diazepam (2 mg/kg *i.p.*) attenuated immobilization stress-induced decrease in decrease in the locomotor activity in a significant manner**.** Treatment with the compound **3a-B** (10 mg/kg *i.p.*) attenuated stress-induced decrease in locomotor activity. However, the comparative effect of trans- isomer on restoration of locomotor activity was significantly less as compared to corresponding cis-isomer at the same dose level of 10 mg/kg. Treatment with compound **3a-B** (2 and 5 mg/kg *i.p.*) failed to attenuate immobilization stress-induced decrease in locomotor activity (Fig. 5).

In the present investigation, immobilization-induced acute stress resulted in significant behavioral alterations including decrease in locomotor activity (decrease in frequency of counts in the actophotometer test); spontaneous and orientation-investigating activities (decrease in head dips and rearings in the hole board test along with decrease in total line crossings and rearings in the open-field test) and alteration of social behavior (decrease in time of following and an increase in time of avoidance in the social-interaction test). The earlier studies from our institute have shown that stress produces behavioral alterations including decrease in locomotor activity, exploratory behavior and social behavior [25].

Table 2
Assessment of social and non-social behavior in the 10 min social interaction test by noting time of following and avoiding the partner for evaluating the anti-stress effect of different doses of compounds **3a-A** and **3a-B**. Results are represented as mean ± S.E.M. With $n = 10$ in each group.

Experimental groups	Social interaction test	
	Following (s)	Avoidance (s)
Normal	498.5 ± 27.5	101.5 ± 27.5
Stress	40.6 ± 12.9[a]	559.4 ± 12.9[a]
Compound **3a-A** (2 mg/kg) in stress	58.6 ± 9.2	541.4 ± 9.2
Compound **3a-A** (5 mg/kg) in stress	145.0 ± 10.9[b]	455.0 ± 10.9[b]
Compound **3a-A** (10 mg/kg) in stress	275.4 ± 85.2[b]	324.6 ± 85.2[b]
Compound **3a-B** (2 mg/kg) in stress	49.5 ± 6.9	550.5 ± 6.9
Compound **3a-B** (5 mg/kg) in stress	58.4 ± 8.3	541.6 ± 8.3
Compound **3a-B** (10 mg/kg) in stress	179.7 ± 12.2	420.3 ± 8.3[b]
Diazepam (2 mg/kg) in stress	295.6 ± 13.5	304.4 ± 13.2[b]

[a] $p < 0.05$ as compared to the normal control.
[b] $p < 0.05$ as compared to the stress control.

In the present study, administration of compound **3a-A** (5 mg/kg and 10 mg/kg) 30 min prior to immobilization stress attenuated immobilization-induced different behavioral alterations in a significant manner. However, its trans- isomer compound **3a-B** attenuated stress-induced behavioral alterations only at higher dose with relatively lesser efficacy at comparable dose level suggesting the prominent anti-stress activity of cis- isomer as compared to its corresponding tran- isomer. Diazepam, employed as a standard anti-stress agent, also attenuated immobilization-stress induced behavioral alterations. Compound **3a-A** and compound **3a-B** (cis- and trans- isomers, respectively) were selected as a representative molecules of synthesized pyrrolo-isoxazole derivatives to explore whether pyrrolo-isoxazole molecule serve as lead with potential anti-stress activity. These compounds contain unsubstituted *C*-phenyl ring while all others are the derivatives of these compounds with different substitutions with electron withdrawing and electron donating at *C*-phenyl ring. Immobilization-induced stress has been the most frequently employed model of stress because stressor is of sufficient intensity to alter most of the stress responsive biological systems. Immobilization is a complex stressor and includes physical as well as psychological dimensions. The struggling and muscular exertion of the mice during the process of immobilization represents a physical dimension; while limited range of movement along with exposure in an open area represents the psychological dimensions [26]. Furthermore, immobilization stress produces behavioral alterations in a reversible manner and animal tend to recover from the stress after a definite time interval depending upon the duration of immobilization stressor. This is important as far as the timing of administration of drug is concerned and the effect of the drug will vary with the change in the time of administration of the drug. The detailed pharmacokinetic parameters of compound **3a-A** including its $t_{1/2}$ are not known, however, the data in hand suggests that drug remain active in the body for sufficient period of time (at least

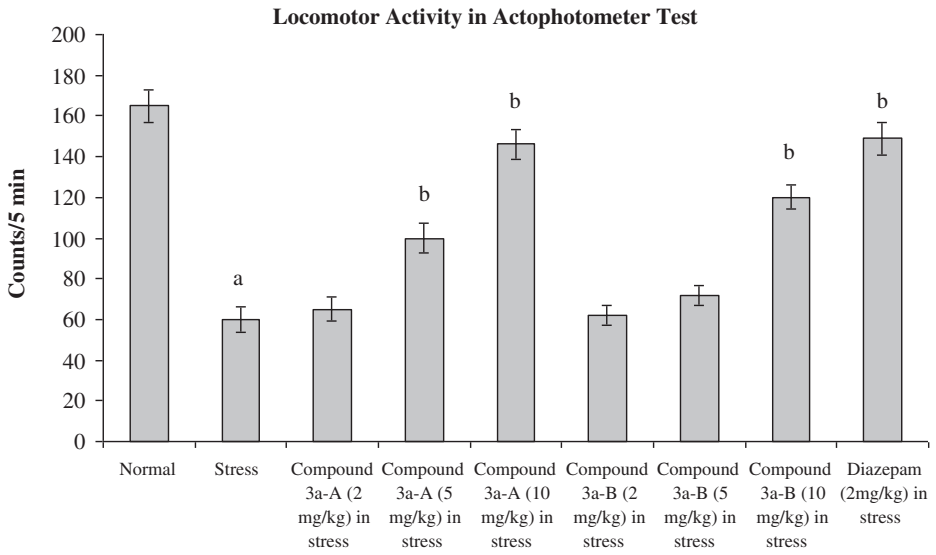


Fig. 5. Assessment of the locomotor activity in terms of counts in 5 min time interval in the actophotometer test for investigating the anti-stress effects of different doses of compounds **3a-A** and **3a-B**. Results are represented as mean ± S.E.M. With $n = 10$ in each group.[a] $p < 0.05$ as compared to the normal control;[b] $p < 0.05$ as compared to the stress control.

3–4 h) including the time of stressor and subsequent behavioral evaluation.

5. Conclusion

A series of novel pyrrolo-isoxazole derivatives were synthesized in good to excellent yields. The compound **3a-A** (cis- isomer) exhibited significant anti-stress activity in immobilization-induced acute stress suggesting that pyrrolo-isoxazole may serve as potential lead for development of effective anti-stress agents.

6. Experimental

6.1. Chemistry

6.1.1. General

All reactions were carried out under a nitrogen atmosphere in oven-dried glassware. Melting points reported are uncorrected. IR spectra were recorded on a Perkin Elmer RX I FTIR Spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker spectrometer at 400 MHz and 300 MHz, respectively, with TMS as internal standard. Mass spectra were recorded on Thermo Scientific, LTQ-XL LCMS. Elemental analysis was carried out using Elementar Vario MICRO cube CHN analyzer.

6.1.2. General procedure for synthesis of azomethine N-oxides

Nitrobenzene (4.16 mL, 41 mmol) and ammonium chloride (2.5 g, 46 mmol) were put into 100 mL water taken in a 500 mL beaker and mixture was stirred with mechanical stirrer. 5.9 g (83 mmol) zinc dust was added in portions to the stirring mixture so that the temperature of mixture does not rise above 60–70 °C. After complete addition of zinc dust, the reduction completed after temperature of mixture began to fall down. Filtered the mixture and to the filtrate was added stoichiometric amount of aromatic aldehyde and stirred the mixture till solid precipitated out. The synthesis of product was confirmed by TLC and further by recording the melting points of the nitrones obtained.

6.1.3. General procedure for synthesis of N-(α-naphthyl)maleimide

Maleic anhydride (4.9 g, 50 mmol) and *N*-(α-naphthyl)amine (7.15 g, 50 mmol) were condensed in toluene (50 mL) to get the maleamic acid. Further the maleamic acid (4.82 g, 20 mmol) was cyclised to maleimide in acetic anhydride (10 mL, 100 mmol) along with catalytic amount of anhydrous sodium acetate (0.82 g, 10 mmol) by refluxing the mixture for 1.5 h on water bath and then poured in ice cold water. Maleimide precipitated out in this manner was characterized by melting point, TLC and IR spectroscopy.

6.1.4. General procedure for cycloadditions

An oven-dried flask was cooled under a stream of nitrogen and charged with azomethine *N*-oxide **1** (0.985 g, 5 mmol), *N*-(α-naphthyl)maleimide **2** (1.115 g, 5 mmol) and sodium dried toluene (25 mL). The flask was equipped with a reflux condenser and the mixture was refluxed for 3.5–4 h until the substrates were consumed as judged by TLC. On completion the reaction mixture was concentrated *in vacuo* and the precipitated compound was filtered. The crude product consists of a mixture of cis and trans isomers which was subjected to flash column chromatography over silica gel (230–400 mesh) using hexane: ethyl acetate mixture as eluent.

*6.1.4.1. cis-Dihydro-5-(naphthalen-1-yl)-2,3-diphenyl-2H-pyrrolo [3,4-d]isoxazole-4,6(5H,6aH)-dione (**3a-A**).* Compound obtained as white solid (0.82 g, 53%); mp: 205–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.3$ (dd, 1H, $J = 8.12$ and 8.76 Hz); 5.0 (d, 1H, $J = 8.48$ Hz); 5.4 (d, 1H, $J = 7.88$ Hz); 6.7–7.9 (m, 17H); ^{13}C NMR (300 MHz, [D_6] DMSO): δ = 54.9, 70.3, 77.2, 118.7, 119.9, 122.8, 124.4, 125.1, 125.7, 126.2, 126.4, 126.6, 126.7, 127.5, 128.0, 128.5, 128.6, 128.8, 129.0, 129.4, 133.5, 134.5, 135.1, 146.7, 147.1, 171.9, 173.8; IR (KBr pellets): 1723, 1786 cm^{-1}(C=O); MS: *m*/*z*: 420 [M]$^+$, Anal. Calcd for $C_{27}H_{20}N_2O_3$: C, 77.14; H, 4.76; N, 6.67, Found: C, 77.28; H, 4.74; N, 6.68.

*6.1.4.2. trans-Dihydro-5-(naphthalen-1-yl)-2,3-diphenyl-2H-pyrrolo [3,4-d]isoxazole-4,6(5H,6aH)-dione (**3a-B**).* Compound obtained as white solid (0.73 g, 47%); mp: 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.3 (dd, 1H, J = 8.28 and 8.88 Hz); 5.0 (d, 1H, J = 8.96 Hz); 5.6 (d, 1H, J = 7.92 Hz); 6.7–7.9 (m, 17H); ^{13}C NMR

(300 MHz, [D$_6$]DMSO): δ = 54.9, 70.5, 77.4, 118.7, 120.1, 122.0, 122.8, 124.3, 125.1, 125.8, 126.6, 126.8, 127.5, 127.8, 128.0, 128.3, 128.5, 128.6, 128.8, 129.4, 133.5, 134.5, 135.1, 146.9, 147.5, 172.1, 174.2; IR (KBr pellets): 1724, 1786 cm^{-1}(C=O); MS: *m*/*z*: 420 [M]$^+$, Anal. Calcd for $C_{27}H_{20}N_2O_3$: C, 77.14; H, 4.76; N, 6.67, Found: C, 77.31; H, 4.74; N, 6.68.

*6.1.4.3. cis-3-(2-tolyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3b-A**).* Compound obtained as white solid (1.10 g, 62%); mp: 220–222 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.2 (S, 3H); 4.3 (dd, 1H, *J* = 8.14 and 8.28 Hz); 5.0 (d, 1H, *J* = 8.48 Hz); 5.4 (d, 1H, *J* = 7.88 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 17.7, 55.1, 65.4, 76.4, 113.7, 119.8, 122.9, 123.6, 124.2, 124.4, 125.5, 126.4, 126.6, 126.9, 127.3, 127.8, 128.3, 129.4, 131.8, 133.0, 133.3, 134.9, 135.2, 142.8, 143.1, 143.7, 172.2, 173.3; IR (KBr pellets): 1725, 1786 cm^{-1}(C=O); MS: *m*/*z*: 434 [M]$^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 77.42; H, 5.07; N, 6.45, Found: C, 77.05; H, 5.16; N, 6.46.

*6.1.4.4. trans-3-(2-tolyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3b-B**).* Compound obtained as white solid (0.67 g, 38%); mp: 205–206 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.2 (S, 3H); 4.3 (dd, 1H, *J* = 8.16 and 8.24 Hz); 5.0 (d, 1H, *J* = 8.92 Hz); 5.5 (d, 1H, *J* = 8.04 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 17.7, 56.0, 65.4, 76.5, 113.9, 120.1, 121.3, 123.6, 124.2, 124.7, 125.1, 125.3, 125.8, 126.1, 126.4, 127.2, 127.6, 128.1, 129.1, 131.9, 133.1, 134.7, 135.8, 143.5, 144.9, 145.3, 173.1, 173.3; IR (KBr pellets): 1725, 1786 cm^{-1}(C=O); MS: *m*/*z*: 434 [M]$^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 77.42; H, 5.07; N, 6.45, Found: C, 77.10; H, 5.09; N, 6.46.

*6.1.4.5. cis-3-(3-tolyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3c-A**).* Compound obtained as white solid (1.14 g, 60%); mp: 222–223 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.2 (S, 3H); 4.3 (dd, 1H, *J* = 8.12 and 8.48 Hz); 5.0 (d, 1H, *J* = 8.40 Hz); 5.4 (d, 1H, *J* = 7.88 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 17.7, 55.1, 65.3, 76.5, 112.5, 120.8, 123.2, 123.7, 124.4, 124.6, 125.2, 126.1, 126.4, 126.6, 127.5, 127.8, 128.0, 129.1, 132.0, 133.2, 133.3, 135.7, 135.9, 146.8, 147.9, 148.1, 173.1, 173.4; IR (KBr pellets): 1725, 1783 cm^{-1}(C=O); MS: *m*/*z*: 434 [M]$^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 77.42; H, 5.07; N, 6.45, Found: C, 77.74; H, 5.22; N, 6.25.

*6.1.4.6. trans-3-(3-tolyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3c-B**).* Compound obtained as white solid (0.76 g, 40%); mp: 202–204 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.2 (S, 3H); 4.3 (dd, 1H, *J* = 8.16 and 8.80 Hz); 5.0 (d, 1H, *J* = 8.92 Hz); 5.6 (d, 1H, *J* = 7.96 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 17.7, 56.0, 65.4, 76.8, 112.3, 120.0, 121.2, 123.6, 124.2, 124.5, 124.9, 125.7, 126.1, 126.2, 126.5, 127.0, 127.7, 127.9, 129.0, 132.0, 133.3, 135.7, 135.9, 146.8, 147.9, 148.0, 172.2, 173.3; IR (KBr pellets): 1725, 1782 cm^{-1}(C=O); MS: *m*/*z*: 434 [M]$^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 77.42; H, 5.07; N, 6.45, Found: C, 77.69; H, 5.21; N, 6.28.

*6.1.4.7. cis-3-(4-tolyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3d-A**).* Compound obtained as white solid (1.08 g, 64%); mp: 215–217 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.2 (S, 3H); 4.3 (dd, 1H, *J* = 8.10 and 8.80 Hz); 5.0 (d, 1H, *J* = 8.48 Hz); 5.4 (d, 1H, *J* = 7.96 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 17.7, 56.0, 65.3, 76.5, 112.3, 120.1, 122.2, 123.1, 123.5, 124.3, 125.2, 125.5, 125.9, 126.3, 127.1, 127.3, 127.6, 128.1, 131.8, 132.9, 133.3, 134.3, 135.0, 146.0, 147.7, 148.1, 173.1, 173.3; IR (KBr pellets): 1724, 1781 cm^{-1}(C=O); MS: *m*/*z*: 434 [M]$^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 77.42; H, 5.07; N, 6.45, Found: C, 77.63; H, 5.01; N, 6.52.

*6.1.4.8. trans-3-(4-tolyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3d-B**).* Compound obtained as white solid (0.61 g, 36%); mp: 206–207 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.2 (S, 3H); 4.3 (dd, 1H, *J* = 8.14 and 8.48 Hz); 5.0 (d, 1H, *J* = 8.92 Hz); 5.6 (d, 1H, *J* = 7.92 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 17.7, 55.7, 65.4, 76.5, 112.3, 120.2, 121.3, 123.0, 123.9, 124.4, 124.7, 125.1, 125.7, 126.2, 126.4, 126.8, 127.2, 127.5, 129.2, 132.3, 133.5, 135.7, 136.9, 145.3, 146.0, 147.1, 172.2, 173.3; IR (KBr pellets): 1724, 1781 cm^{-1}(C=O); MS: *m*/*z*: 434 [M]$^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 77.42; H, 5.07; N, 6.45, Found: C, 77.67; H, 4.99; N, 6.59.

*6.1.4.9. cis-3-(2-chlorophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3e-A**).* Compound obtained as white solid (1.18 g, 62%); mp: 189–191 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.2 (dd, 1H, *J* = 8.16 and 8.48 Hz); 5.0 (d, 1H, *J* = 8.40 Hz); 5.3 (d, 1H, *J* = 7.92 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 56.8, 68.2, 77.2, 116.8, 118.0, 120.6, 122.3, 122.9, 123.5, 124.1, 125.2, 125.5, 126.2, 126.4, 126.6, 127.0, 127.3, 127.6, 128.2, 128.8, 129.5, 131.4, 133.5, 145.9, 146.3, 172.7, 173.8; IR (KBr pellets): 1724, 1784 cm^{-1}(C=O); MS: *m*/*z*: 454 [M]$^+$, 456 [M+2]$^+$, Anal. Calcd for $C_{27}H_{19}N_2O_3Cl$: C, 71.36; H, 4.18; N, 6.17, Found: C, 70.99; H, 4.22; N, 6.02.

*6.1.4.10. trans-3-(2-chlorophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3e-B**).* Compound obtained as white solid (0.72 g, 38%); mp: 180–182 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.2 (dd, 1H, *J* = 8.12 and 8.38 Hz); 5.0 (d, 1H, *J* = 9.12 Hz); 5.5 (d, 1H, *J* = 7.88 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 57.0, 68.7, 77.2, 116.9, 118.2, 120.8, 122.5, 123.1, 123.7, 124.1, 125.1, 125.5, 126.0, 126.2, 126.4, 126.8, 127.0, 127.4, 128.2, 128.9, 129.7, 133.6, 135.4, 146.7, 148.1, 173.4, 173.9; IR (KBr pellets): 1724, 1784 cm^{-1}(C=O); MS: *m*/*z*: 454 [M]$^+$, 456 [M+2]$^+$, Anal. Calcd for $C_{27}H_{19}N_2O_3Cl$: C, 71.36; H, 4.18; N, 6.17, Found: C, 71.04; H, 4.23; N, 6.04.

*6.1.4.11. cis-3-(3-chlorophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3f-A**).* Compound obtained as white solid (1.25 g, 60%); mp: 192–193 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.2 (dd, 1H, *J* = 8.12 and 8.92 Hz); 5.0 (d, 1H, *J* = 8.40 Hz); 5.3 (d, 1H, *J* = 7.88 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 55.1, 67.4, 77.0, 117.3, 118.7, 120.5, 122.4, 123.1, 123.6, 124.3, 124.7, 125.6, 125.7, 126.5, 127.3, 128.2, 128.5, 128.8, 129.0, 129.3, 129.7, 133.5, 134.7, 146.1, 147.9, 172.9, 174.1; IR (KBr pellets): 1714, 1783 cm^{-1}(C=O); MS: *m*/*z*: 454 [M]$^+$, 456 [M+2]$^+$, Anal. Calcd for $C_{27}H_{19}N_2O_3Cl$: C, 71.36; H, 4.18; N, 6.17, Found: C, 71.16; H, 4.13; N, 6.19.

*6.1.4.12. trans-3-(3-chlorophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3f-B**).* Compound obtained as white solid (0.83 g, 40%); mp: 185–186 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.3 (dd, 1H, *J* = 8.12 and 8.88 Hz); 5.0 (d, 1H, *J* = 9.00 Hz); 5.5 (d, 1H, *J* = 8.00 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 55.8, 68.0, 77.2, 117.5, 118.9, 120.7, 122.6, 123.2, 123.6, 124.4, 124.7, 125.3, 125.7, 126.0, 127.1, 127.7, 128.3, 128.6, 128.9, 129.1, 129.4, 133.4, 134.8, 146.3, 148.1, 173.4, 174.2; IR (KBr pellets): 1714, 1786 cm^{-1}(C=O); MS: *m*/*z*: 454 [M]$^+$, 456 [M+2]$^+$, Anal. Calcd for $C_{27}H_{19}N_2O_3Cl$: C, 71.36; H, 4.18; N, 6.17, Found: C, 71.62; H, 4.21; N, 6.18.

*6.1.4.13. cis-3-(4-chlorophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3g-A**).* Compound obtained as white solid (1.26 g, 63%); mp: 222–223 °C; ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 4.2 (dd, 1H, J = 8.12 and 8.40 Hz); 5.0 (d, 1H, J = 8.48 Hz); 5.3 (d, 1H, J = 7.88 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.9, 70.3, 77.2, 118.1, 119.3, 122.3, 123.8, 124.5, 125.3, 125.7, 126.6, 127.5, 127.7, 128.0, 128.3, 128.6, 128.8, 129.1, 129.3, 129.6, 130.8, 133.5, 135.4, 146.3, 147.1, 172.9, 174.1; IR (KBr pellets): 1719, 1784 cm^{-1}(C═O); MS: m/z: 454 $[M]^+$, 456 $[M+2]^+$, Anal. Calcd for $C_{27}H_{19}N_2O_3Cl$: C, 71.36; H, 4.18; N, 6.17, Found: C, 71.09; H, 4.08; N, 6.29.

*6.1.4.14. trans-3-(4-chlorophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3g-B**).* Compound obtained as white solid (0.74 g, 37%); mp: 210–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.3 (dd, 1H, J = 8.16 and 8.80 Hz); 5.0 (d, 1H, J = 9.12 Hz); 5.5 (d, 1H, J = 8.04 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 55.3, 68.7, 77.2, 118.7, 120.3, 121.1, 123.6, 124.2, 124.5, 125.5, 126.2, 127.3, 127.7, 128.1, 128.3, 128.5, 128.7, 129.1, 129.4, 129.7, 130.5, 132.9, 135.1, 145.7, 146.8, 173.4, 174.2; IR (KBr pellets): 1720, 1784 cm^{-1}(C═O); MS: m/z: 454 $[M]^+$, 456 $[M+2]^+$, Anal. Calcd for $C_{27}H_{19}N_2O_3Cl$: C, 71.36; H, 4.18; N, 6.17, Found: C, 71.13; H, 4.09; N, 6.31.

*6.1.4.15. cis-3-(2-hydroxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3h-A**).* Compound obtained as white solid (1.20 g, 64%); mp: 232–233 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.3 (dd, 1H, J = 8.12 and 8.76 Hz); 5.1 (d, 1H, J = 8.40 Hz); 5.3 (d, 1H, J = 7.92 Hz); 6.7–7.9 (m, 16H); 9.9 (s, 1H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.9, 70.5, 77.0, 118.7, 122.0, 122.4, 124.1, 124.8, 125.3, 125.6, 126.3, 127.4, 127.6, 127.8, 128.0, 128.3, 128.5, 128.7, 128.9, 129.4, 133.5, 134.2, 134.7, 146.3, 147.7, 171.7, 173.9; IR (KBr pellets): 1703, 1782 cm^{-1}(C═O); MS: m/z: 436 $[M]^+$, Anal. Calcd for $C_{27}H_{20}N_2O_4$: C, 74.31; H, 4.59; N, 6.42, Found: C, 74.53; H, 4.57; N, 6.35.

*6.1.4.16. trans-3-(2-hydroxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3h-B**).* Compound obtained as white solid (0.67 g, 36%); mp: 205–206 °C; 1H NMR (400 MHz, CDCl3): δ = 4.3 (dd, 1H, J = 8.14 and 8.68 Hz); 5.1 (d, 1H, J = 8.96 Hz); 5.5 (d, 1H, J = 7.96 Hz); 6.7–7.9 (m, 16H); 9.9 (s, 1H); 13C NMR (300 MHz, [D6]DMSO): δ = 54.9, 70.6, 77.2, 119.8, 122.8, 123.3, 124.4, 125.1, 125.6, 126.3, 127.0, 127.4, 127.6, 127.9, 128.1, 128.4, 128.6, 128.7, 129.0, 133.5, 134.2, 134.9, 136.1, 146.8, 148.1, 171.9, 174.1; IR (KBr pellets): 1703, 1782 cm^{-1}(C═O); MS: m/z: 436 [M]+, Anal. Calcd for C27H20N2O4: C, 74.31; H, 4.59; N, 6.42, Found: C, 74.49; H, 4.56; N, 6.32.

*6.1.4.17. cis-3-(3-hydroxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3i-A**).* Compound obtained as white solid (1.04 g, 58%); mp: 197–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.3 (dd, 1H, J = 8.16 and 8.76 Hz); 5.1 (d, 1H, J = 8.48 Hz); 5.3 (d, 1H, J = 7.92 Hz); 6.7–7.9 (m, 16H); 9.9 (s, 1H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.9, 70.5, 77.0, 118.7, 121.9, 124.3, 125.7, 125.9, 126.2, 126.6, 126.8, 127.4, 127.7, 128.0, 128.2, 128.4, 128.6, 128.7, 128.9, 129.1, 133.2, 134.9, 146.3, 146.5, 147.1, 171.7, 173.9; IR (KBr pellets): 1706, 1784 cm^{-1}(C═O); MS: m/z: 436 $[M]^+$, Anal. Calcd for $C_{27}H_{20}N_2O_4$: C, 74.31; H, 4.59; N, 6.42, Found: C, 74.55; H, 4.63; N, 6.44.

*6.1.4.18. trans-3-(3-hydroxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3i-B**).* Compound obtained as white solid (0.75 g, 42%); mp: 192–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.3 (dd, 1H, J = 8.14 and 8.78 Hz); 5.1 (d, 1H, J = 8.92 Hz); 5.5 (d, 1H, J = 8.04 Hz); 6.8–7.9 (m, 16H); 9.9 (s, 1H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.9, 70.6, 77.2, 119.9, 122.8, 125.1, 125.5, 125.9, 126.3, 126.5, 126.7, 127.0, 127.5, 127.8, 128.2, 128.5, 128.6, 128.8, 129.1, 129.4, 133.4, 134.5, 135.1, 146.9, 147.4, 171.9, 174.1; IR (KBr pellets): 1704, 1784 cm^{-1}(C═O); MS: m/z: 436 $[M]^+$, Anal. Calcd for $C_{27}H_{20}N_2O_4$: C, 74.31; H, 4.59; N, 6.42, Found: C, 74.59; H, 4.63; N, 6.47.

*6.1.4.19. cis-3-(4-hydroxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3j-A**).* Compound obtained as white solid (1.02 g, 53%); mp: 210–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.3 (dd, 1H, J = 8.16 and 8.48 Hz); 5.1 (d, 1H, J = 8.44 Hz); 5.3 (d, 1H, J = 7.88 Hz); 6.8–7.9 (m, 16H); 9.9 (s, 1H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.9, 70.3, 77.2, 119.3, 122.1, 122.6, 124.3, 125.0, 125.6, 126.2, 127.4, 127.6, 127.9, 128.1, 128.3, 128.5, 128.7, 128.9, 129.3, 132.9, 134.2, 134.9, 145.7, 146.8, 147.4, 172.1, 173.3; IR (KBr pellets): 1706, 1785 cm^{-1}(C═O); MS: m/z: 436 $[M]^+$, Anal. Calcd for $C_{27}H_{20}N_2O_4$: C, 74.31; H, 4.59; N, 6.42, Found: C, 74.06; H, 4.59; N, 6.39.

*6.1.4.20. trans-3-(4-hydroxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3j-B**).* Compound obtained as white solid (0.90 g, 47%); mp: 197–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.3 (dd, 1H, J = 8.12 and 8.42 Hz); 5.0 (d, 1H, J = 8.96 Hz); 5.6 (d, 1H, J = 7.96 Hz); 6.8–7.9 (m, 16H); 9.9 (s, 1H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 55.0, 70.5, 77.2, 118.9, 122.0, 122.6, 124.4, 125.1, 125.7, 126.4, 126.6, 126.9, 127.1, 127.5, 127.7, 128.0, 128.3, 128.5, 128.7, 129.0, 129.4, 133.5, 135.1, 146.2, 147.6, 171.9, 174.0; IR (KBr pellets): 1703, 1786 cm^{-1}(C═O); MS: m/z: 436 $[M]^+$, Anal. Calcd for $C_{27}H_{20}N_2O_4$: C, 74.31; H, 4.59; N, 6.42, Found: C, 74.11; H, 4.62; N, 6.38.

*6.1.4.21. cis-3-(2-methoxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3k-A**).* Compound obtained as white solid (1.02 g, 58%); mp: 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.9 (S, 3H, OCH_3); 4.2 (dd, 1H, J = 8.14 and 8.76 Hz); 5.0 (d, 1H, J = 8.40 Hz); 5.3 (d, 1H, J = 7.96 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.8, 65.3, 70.5, 77.3, 118.8, 120.0, 122.1, 122.8, 124.3, 125.1, 125.8, 126.3, 126.7, 127.5, 127.7, 128.0, 128.3, 128.6, 128.9, 129.1, 129.4, 133.5, 134.5, 135.1, 146.9, 147.4, 171.9, 173.8; IR (KBr pellets): 1705, 1781 cm^{-1}(C═O); MS: m/z: 450 $[M]^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 74.67; H, 4.89; N, 6.22, Found: C, 74.71; H, 4.86; N, 6.24.

*6.1.4.22. trans-3-(2-methoxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3k-B**).* Compound obtained as white solid (0.74 g, 42%); mp: 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.9 (S, 3H, OCH_3); 4.2 (dd, 1H, J = 8.20 and 8.42 Hz); 5.1 (d, 1H, J = 9.00 Hz); 5.5 (d, 1H, J = 7.92 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.9, 65.4, 70.3, 77.4, 118.7, 119.9, 122.0, 122.8, 124.4, 125.9, 126.2, 126.6, 127.5, 127.8, 128.0, 128.2, 128.5, 128.7, 128.9, 129.1, 133.4, 133.7, 134.5, 135.5, 146.2, 147.0, 172.1, 174.2; IR (KBr pellets): 1705, 1783 cm^{-1}(C═O); MS: m/z: 450 $[M]^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 74.67; H, 4.89; N, 6.22, Found: C, 74.76; H, 4.88; N, 6.24.

*6.1.4.23. cis-3-(3-methoxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3l-A**).* Compound obtained as white solid (1.17 g, 62%); mp: 208–210 °C; ^{1}H NMR (400 MHz, CDCl3): δ = 3.9 (S, 3H, OCH3); 4.2 (dd, 1H, J = 8.18 and 8.48 Hz); 5.0 (d, 1H, J = 8.48 Hz); 5.3 (d, 1H, J = 7.92 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.9, 65.4, 70.5, 77.2, 119.7, 119.9, 122.1, 122.9, 124.3, 124.6, 125.1, 126.0, 127.2, 127.5, 127.9, 128.1, 128.4, 128.7, 129.0, 129.3, 132.9, 133.2, 133.9, 145.7, 146.0, 146.4, 172.1, 173.3; IR (KBr pellets): 1703, 1782 cm^{-1}(C═O); MS: m/z: 450 $[M]^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 74.67; H, 4.89; N, 6.22, Found: C, 74.89; H, 4.91; N, 6.17.

*6.1.4.24. trans-3-(3-Methoxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3l-B**).* Compound obtained as white solid (0.72 g, 38%); mp: 186–187 °C; ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 3.9 (S, 3H, OCH_3); 4.2 (dd, 1H, J = 8.20 and 8.48 Hz); 5.1 (d, 1H, J = 8.96 Hz); 5.5 (d, 1H, J = 7.96 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 55.1, 65.4, 70.3, 77.3, 119.7, 120.0, 122.1, 123.2, 123.5, 124.6, 124.9, 125.2, 125.6, 126.1, 126.5, 127.0, 127.4, 127.7, 128.0, 129.1, 132.0, 133.2, 133.5, 135.7, 146.8, 147.9, 173.1, 173.4; IR (KBr pellets): 1703, 1783 cm^{-1}(C═O); MS: m/z: 450 $[M]^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 74.67; H, 4.89; N, 6.22, Found: C, 74.87; H, 4.90; N, 6.17.

*6.1.4.25. cis-3-(4-Methoxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3m-A**).* Compound obtained as white solid (1.11 g, 58%); mp: 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.9 (S, 3H, OCH_3); 4.2 (dd, 1H, J = 8.16 and 8.76 Hz); 5.0 (d, 1H, J = 8.48 Hz); 5.3 (d, 1H, J = 7.88 Hz); 6.7–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.9, 65.3, 70.5, 77.2, 118.7, 119.9, 122.0, 122.6, 124.3, 125.0, 125.6, 126.2, 127.4, 127.7, 128.0, 128.1, 128.3, 128.5, 128.7, 128.9, 133.5, 134.2, 134.9, 146.3, 146.5, 147.1, 171.7, 173.9; IR (KBr pellets): 1703, 1783 cm^{-1}(C═O); MS: m/z: 450 $[M]^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 74.67; H, 4.89; N, 6.22, Found: C, 74.81; H, 4.84; N, 6.07.

*6.1.4.26. trans-3-(4-methoxyphenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3m-B**).* Compound obtained as white solid (0.80 g, 42%); mp: 192–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.9 (S, 3H, OCH_3); 4.2 (dd, 1H, J = 8.18 and 8.52 Hz); 5.1 (d, 1H, J = 9.00 Hz); 5.5 (d, 1H, J = 7.92 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 54.9, 65.4, 70.3, 77.2, 118.7, 119.8, 122.1, 122.6, 124.4, 125.1, 125.6, 125.9, 126.3, 126.5, 127.3, 127.6, 128.1, 128.3, 128.6, 129.0, 132.5, 132.8, 133.1, 133.5, 134.2, 135.0, 171.9, 174.0; IR (KBr pellets): 1704, 1783 cm^{-1}(C═O); MS: m/z: 450 $[M]^+$, Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 74.67; H, 4.89; N, 6.22, Found: C, 74.81; H, 4.84; N, 6.08.

*6.1.4.27. cis-3-(2-Nitrophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3n-A**).* Compound obtained as white solid (1.19 g, 64%); mp: 206–207 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.2 (dd, 1H, J = 8.14 and 8.88 Hz); 5.0 (d, 1H, J = 8.40 Hz); 5.4 (d, 1H, J = 7.92 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 56.5, 68.3, 76.9, 112.7, 113.5, 120.4, 121.3, 121.6, 121.9, 122.2, 122.6, 123.3, 124.0, 124.9, 125.7, 126.2, 126.7, 127.5, 127.7, 128.1, 129.4, 133.5, 145.4, 146.0, 148.3, 172.9, 174.0; IR (KBr pellets): 1725, 1786 cm^{-1}(C═O); MS: m/z: 465 $[M]^+$, Anal. Calcd for $C_{27}H_{19}N_3O_5$: C, 69.68; H, 4.09; N, 9.03, Found: C, 69.34; H, 4.11; N, 9.24.

*6.1.4.28. trans-3-(2-Nitrophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3n-B**).* Compound obtained as white solid (0.67 g, 36%); mp: 184–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.2 (dd, 1H, J = 8.14 and 8.76 Hz); 5.0 (d, 1H, J = 8.96 Hz); 5.6 (d, 1H, J = 7.88 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 56.7, 68.3, 77.0, 112.9, 113.7, 121.3, 122.5, 122.7, 123.3, 123.6, 124.1, 124.5, 124.9, 125.1, 125.6, 126.0, 127.3, 127.5, 127.7, 128.7, 129.9, 133.5, 145.9, 146.1, 147.3, 173.4, 174.1; IR (KBr pellets): 1725, 1787 cm^{-1}(C═O); MS: m/z: 465 $[M]^+$, Anal. Calcd for $C_{27}H_{19}N_3O_5$: C, 69.68; H, 4.09; N, 9.03, Found: C, 69.36; H, 4.13; N, 9.27.

*6.1.4.29. cis-3-(3-Nitrophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3o-A**).* Compound obtained as white solid (1.05 g, 58%); mp: 215–216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.2 (dd, 1H, J = 8.18 and 8.74 Hz); 5.0 (d, 1H, J = 8.48 Hz); 5.4 (d, 1H, J = 7.88 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 56.9, 69.7, 77.2, 112.3, 120.5, 120.8, 121.1, 121.6, 121.9, 123.2, 123.5, 123.9, 124.3, 124.6, 125.2, 126.1, 126.5, 127.1, 127.7, 127.9, 129.0, 132.1, 135.3, 146.8, 148.0, 172.9, 174.1; IR (KBr pellets): 1723, 1781 cm^{-1}(C═O); MS: m/z: 465 $[M]^+$, Anal. Calcd for $C_{27}H_{19}N_3O_5$: C, 69.68; H, 4.09; N, 9.03, Found: C, 69.93; H, 4.43; N, 8.97.

*6.1.4.30. trans-3-(3-Nitrophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3o-B**).* Compound obtained as white solid (0.76 g, 42%); mp: 202–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.2 (dd, 1H, J = 8.20 and 8.62 Hz); 5.0 (d, 1H, J = 9.12 Hz); 5.6 (d, 1H, J = 7.92 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 56.9, 69.1, 77.3, 112.5, 120.0, 121.1, 123.5, 124.2, 124.4, 124.6, 125.1, 126.1, 126.4, 126.6, 127.5, 127.8, 128.0, 132.2, 133.4, 133.7, 134.9, 136.1, 146.8, 147.1, 147.7, 173.4, 174.2; IR (KBr pellets): 1724, 1783 cm^{-1}(C═O); MS: m/z: 465 $[M]^+$, Anal. Calcd for $C_{27}H_{19}N_3O_5$: C, 69.68; H, 4.09; N, 9.03, Found: C, 69.91; H, 4.39; N, 8.98.

*6.1.4.31. cis-3-(4-Nitrophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3p-A**).* Compound obtained as white solid (1.00 g, 60%); mp: 238–240 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.2 (dd, 1H, J = 8.14 and 8.40 Hz); 5.0 (d, 1H, J = 8.48 Hz); 5.4 (d, 1H, J = 7.88 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 56.8, 68.2, 77.2, 113.9, 114.7, 121.4, 122.3, 122.5, 122.7, 123.3, 124.9, 125.1, 125.7, 126.1, 126.6, 127.0, 127.7, 127.9, 128.3, 129.0, 129.3, 129.5, 133.4, 146.0, 146.9, 172.8, 173.9; IR (KBr pellets): 1725, 1787 cm^{-1}(C═O); MS: m/z: 465 $[M]^+$, Anal. Calcd for $C_{27}H_{19}N_3O_5$: C, 69.68; H, 4.09; N, 9.03, Found: C, 69.83; H, 4.05; N, 9.11.

*6.1.4.32. trans-3-(4-Nitrophenyl)-dihydro-5-(naphthalen-1-yl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**3p-B**).* Compound obtained as white solid (0.67 g, 40%); mp: 220–222 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.2 (dd, 1H, J = 8.18 and 8.42 Hz); 5.0 (d, 1H, J = 9.12 Hz); 5.6 (d, 1H, J = 7.96 Hz); 6.8–7.9 (m, 16H); ^{13}C NMR (300 MHz, [D_6]DMSO): δ = 56.9, 68.7, 77.3, 114.1, 114.8, 121.5, 122.4, 122.7, 123.3, 123.8, 124.1, 124.6, 125.1, 125.8, 126.3, 126.6, 127.0, 127.9, 128.3, 128.7, 129.4, 133.5, 143.5, 145.1, 146.7, 173.3, 174.1; IR (KBr pellets): 1724, 1787 cm^{-1}(C═O); MS: m/z: 465 $[M]^+$, Anal. Calcd for $C_{27}H_{19}N_3O_5$: C, 69.68; H, 4.09; N, 9.03, Found: C, 69.87; H, 4.10; N, 9.11.

6.2. Biological evaluation

6.2.1. Animals

Swiss albino male mice, weighing 20–25 g, were employed in the present study. Animals were fed on standard laboratory diet and water *ad libitum*. The experimental protocol was approved by the Institutional Animal Ethics Committee and care of the animals was carried out as per the guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), Ministry of Environment and Forests, Government of India (Reg.No.-107/1999/CPCSEA).

6.2.2. Induction of acute immobilization stress

Acute stress was produced as per the method described by Kvetnansky and Mikulai [27]. Mice were immobilized in the prone position with all four limbs fixed to the immobilization board with adhesive tape. The head was also fixed with a metal loop over the neck area, with a consequent limitation of head motion. The mice were kept immobilized in this position for 2 h for inducing acute stress.

6.2.3. Behavioral measurements

All the animals were acclimatized for 5 min on behavioral test equipments for three days before initiating the actual experimental protocol. It is necessary to acclimatize the animals to the test apparatus in the behavioral studies to avoid potentially confounding effects induced by novelty of the testing apparatus that in-turn reduces the variation in the experimental data. After exposure of

immobilization stress, the battery of behavioral tests were performed in animals with the sequence of actophotometer, the hole board, the open field, and the social interaction with a time gap of 5 min between the successive behavioral tests. All behavioral test equipments were cleaned after each test.

6.2.3.1. Hole board test. The hole board test was employed to assess the exploratory behavior of animals. The hole board consisted of a wooden box measuring 68 cm × 68 cm. The walls were 40 cm high, and the box was raised 28 cm above the ground on a stand. Four holes (4 cm in diameter) were cut into the floor of the apparatus: each hole was 28 cm from a corner of the box along the diagonal from the corner to the centre. The floor of the box was marked out into four outer areas and one central area using black masking tape. The central area was delineated by four lines of tape each 20 cm from one of the walls, while the four outer areas were marked out by diagonal lines of tape running from the corners of the floor to the corners of the central square. The four holes were thus located at the corners of the central area. The animals were assessed for 10 min during which the number of rearing (representing exploration in the novel surroundings) and number of head dips were recorded [28].

6.2.3.2. Open field test. The open field test has been considered as a non-conditioned anxiety test based on the creation of a conflict between the exploratory drive of the rat and its innate fear to exposure to an open area. The open field test has been employed to assess the spontaneous activity, general exploration and ambulation of the rodents. The open field consisted of a wooden box 90 cm × 90 cm × 38 cm positioned in a dimly lighted room. The walls were painted black, while the floor was painted white and was divided by 1 cm wide black lines into 25 squares of 17 cm × 17 cm (16 peripheral squares and 9 central squares). The mice were placed in the centre of the open field for 10 min and during this period; the number of line crossings and rearings were noted [29].

6.2.3.3. Social interaction test. The social interaction test has been widely used as an anxiety related paradigm. The social interaction test was carried out in the same box in which open field test was performed. During the 10 min test, the duration of social behaviors was noted in terms of following the partner which also included sniffing the partner, contact interaction (physical contact with mutual responses and orientation toward the other), climbing over or burrowing under it, and walking around it. A mouse is considered to be socially interacting when in close proximity to, and facing the test partner. The remaining time interval was considered as avoidance of partner and non-social behavior which included actively turning away, keeping the approaching interaction partner at distance with forepaws in an upright posture, freezing when approached by the conspecific animal, self-grooming and remaining alone [25].

6.2.3.4. Actophotometer test. The locomotor activity was used as an index of wakefulness (alertness) of mental activity and was assessed using an actophotometer. The locomotor activity was assessed in terms of counts per 5 min [30,31].

6.2.4. Experimental protocol

Twelve groups, each comprising ten Swiss albino mice, were employed in the present study.

6.2.4.1. Group I: normal control. The mice were not subjected to any type of stressor and the locomotor, the exploratory and the social interaction activities were noted in these normal mice.

6.2.4.2. Group II: stress control. The mice were subjected to single episode of immobilization stress and the different behavioral tests were performed as described in group I.

*6.2.4.3. Group III, IV, V: compound **3a-A** (2, 5 and 10 mg/kg) in stress control.* The synthesized compound **3a-A** was administered in different doses (2, 5 and 10 mg/kg) 60 min before subjecting the animals to stress and the different behavioral tests were performed as described in group I.

*6.2.4.4. Group VI, VII, VIII: compound **3a-B** (2, 5 and 10 mg/kg) in stress control.* The synthesized compound **3a-B** was administered in different doses (2, 5 and 10 mg/kg) 60 min before subjecting the animals to stress and the different behavioral tests were performed as described in group I.

6.2.4.5. Group IX: diazepam (2 mg/kg i.p.) in stress control. Diazepam was employed as standard drug and was administered (2 mg/kg) 60 min before subjecting the animals to stress and the different behavioral tests were performed as described in group I.

*6.2.4.6. Group X: compound **3a-A** (10 mg/kg) per se.* The synthesized compound **3a-A** (**10 mg/kg**) was administered in normal animals and the different behavioral tests were performed as described in group I.

*6.2.4.7. Group XI: compound **3a-B** (10 mg/kg) per se.* The synthesized compound **3a-B** (**10 mg/kg**) was administered in normal animals and the different behavioral tests were performed as described in group I.

6.2.4.8. Group XII: DMSO (vehicle) in stress control. The vehicle for compound **3a-A** and compound **3a-B** was administered 60 min before subjecting the animals to stress and the different behavioral tests were performed as described in group I.

6.2.5. Statistical analysis

The results were expressed as mean ± standard error of means (S.E.M.). The results were analyzed using one-way ANOVA followed by *post-hoc* analysis using Tukey's Multiple Comparison test for comparison between different groups. The $p < 0.05$ was considered to be statistically significant.

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