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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of novel isoxazolines via 1,3-dipolar cycloaddition and evaluation of anti-stress activity

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Abstract We have synthesized a series of novel isoxazolines via 1,3-dipolar cycloaddition of in situ generated nitrile oxide from 2,4-dimethoxy benzaldoxime and naphthaldehyde oxime with 4-allyl-2-methoxyphenol derivatives. The synthesized compounds were evaluated for anti-stress activity in acute stress (AS) induced peripheral changes. Adult male Sprague–Dawley rats, subjected to AS, cause a significant increase in gastric ulceration, adrenal gland weight, plasma glucose, corticosterone levels, and creatine kinase activity. Compounds **3d**, **3g**, **5b**, **5c**, **5d**, and **5g** displayed most promising anti-stress effect by reverting these peripheral stress parameters at a dose of 40 mg/kg p.o.

Keywords Isoxazoline · 1,3-Dipolar cycloaddition · Acute stress · Corticosterone · Ulcer

Introduction

Hyperactivity of hypothalamic–pituitary–adrenal axis (HPA) during stressful conditions has been implicated in etiopathogenesis of various disorders of central and peripheral systems like hypertension, coronary heart disease (Roy *et al.*, 2001), gastric ulcers (Yadin and Thomas, 1996), immunosuppression (Purett, 2001), metabolic disorders like diabetes (Fitzpatrick *et al.*, 1992), reproductive dysfunction (Dabson and Smith, 2000), mental depression and memory loss (Gareri *et al.*, 2000). Thus, the treatment of stress pathologies is of great concern because of their increasing incidence (McEwen and Wingfield, 2003). Due to the limitations of tolerance, sedation and physical dependence on prolonged use of modern anti-stress drugs; the identification of new effective and safe anti-stress agents is desperately needed.

Previous studies showed that several isoxazoline moieties possessed a wide spectrum of activities like PTP1B inhibitory activity (Ahmad *et al.*, 2006), antimicrobial (Gaonkar *et al.*, 2007), anti-influenza virus (Kai *et al.*, 2001), antifungal (Basappa *et al.*, 2003), glycoprotein IIb/IIIa receptor antagonists (Sielecki *et al.*, 2001), anti-HIV (Ichiba *et al.*, 1993), spermicidal and anti-HIV (Srivastava *et al.*, 1999), analgesic and anti-inflammatory (Habeeb *et al.*, 2001), and β-adrenergic receptor antagonist properties (Conti *et al.*, 1998). However, their role during stressful condition is unknown. We report herein the synthesis of series of new 3,5-disubstituted isoxazolines and their evaluation for anti-stress activity under acute stress (AS) condition in relation to the peripheral (ulcer severity and adrenal hypertrophy) and biochemical changes [glucose, creatine kinase (CK), and corticosterone].

Results and discussion

Chemistry

The starting materials, aldoximes **1** (Maurya *et al.*, 2008) and **4** (Yamada *et al.*, 2006), were prepared from the

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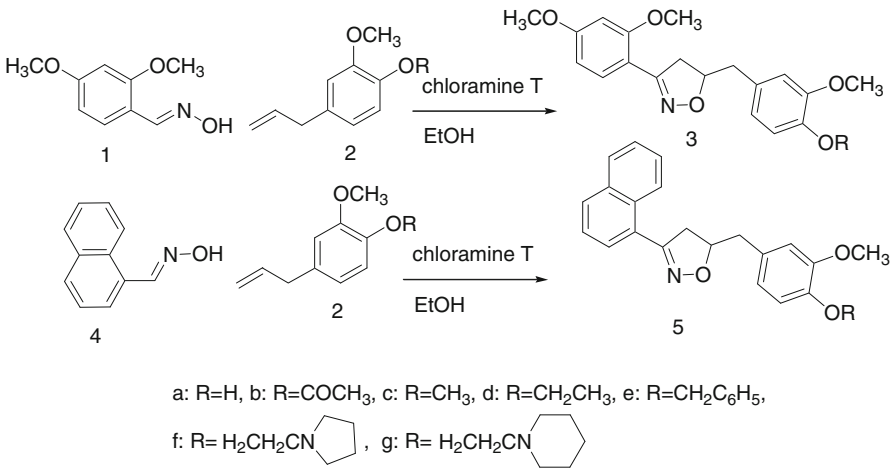
Scheme 1 Synthesis of isoxazoline compounds by altering the substituent in 4-allyl-2-methoxy-phenol



a: R=H, b: R=$COCH_3$, c: R=CH_3, d: R=CH_2CH_3, e: R=$CH_2C_6H_5$,

f: R= H_2CH_2CN , g: R= H_2CH_2CN

2,4-dimethoxy benzaldehyde and 1-naphthaldehyde. The olefin **2b** was prepared by acetylating **2** with acetic anhydride and pyridine. The olefins **2c–g** were prepared in almost quantitative yield by treatment of **2** with methyl iodide, ethyl iodide, benzyl bromide, *N*-(2-chloroethyl) pyrrolidine hydrochloride, and *N*-(2-chloroethyl) piperidine hydrochloride in presence of K_2CO_3 in dry acetone, respectively. The cycloaddition reaction of oximes **1**, **4** with olefins **2** in presence of chloramines-T (Hassner and Rai, 1989) afforded new isoxazolines **3a–d**, **5a–d** in 77–88% yields (Scheme 1). The structure of cycloadducts was determined by elemental analysis and their spectral data.

Biological activity

We select immobilization stressor in our AS model because of the fact that it produces both physical as well as inescapable psychological stress (Marty *et al.*, 1997). All the synthesized isoxazolines (**3a–g**, **5a–g**) were screened for anti-stress activity in AS model at a dose of 40 mg/kg p.o. body weight (Table 1) (Gupta *et al.*, 2007). We used PQ at a dose of 100 mg/kg p.o. body weight as a standard drug (Rai *et al.*, 2003). AS ($F(16, 85) = 6.397$, $P < 0.001$) resulted in significant increase in the scores of ulcer index when compared to non-stress control (NS) group. So the stimulation of Para ventricular nucleus of hypothalamus increased intestinal motility, acid secretion, and group of other factors during stressful conditions (Glavin *et al.*, 1991; Mayer, 2000). Pretreatment of **3b** ($P < 0.05$), **3d** ($P < 0.01$), **3e** ($P < 0.05$), **3g** ($P < 0.05$), **5b** ($P < 0.05$), **5c** ($P < 0.01$), **5d** ($P < 0.05$), **5g** ($P < 0.05$), and PQ ($P < 0.01$) significantly decreased mean ulcer score when compared to AS group, whereas administration of **3a**, **3c**, **3f**, **5a**, **5e**, **5f** produced no significant changes in ulcer index as compared to AS group. Also exposure to AS ($F(16, 85) = 9.38$, $P < 0.001$) significantly increased the adrenal gland weight when compared to NS group. These results are in accordance to a number of studies, suggesting that stress caused an increased adrenocorticoid secretion, plasma corticosterone levels, and enlarged pituitary and adrenal size (Dhabhar *et al.*, 1997). Pretreatment of **3b** ($P < 0.001$), **3d** ($P < 0.01$), **3e** ($P < 0.05$), **3g** ($P < 0.01$), **5b** ($P < 0.01$), **5c** ($P < 0.01$), **5d** ($P < 0.05$), **5g** ($P < 0.001$), and PQ ($P < 0.001$) significantly normalized the increased adrenal gland weight, whereas administration of **3a**, **3c**, **3f**, **5a**, **5e**, and **5f** produced no significant changes as compared to AS group (Table 1).

AS exposure resulted in a significant increase in the plasma glucose level ($F(16, 85) = 14.09$, $P < 0.001$), CK activity ($F(16, 85) = 10.98$, $P < 0.001$), and corticosterone levels ($F(16, 85) = 12.95$, $P < 0.001$) when compared to NS group. This could be attributed to the release of glucocorticoids as a result of HPA axis stimulation, to compensate the initial demand of energy (Mason, 1968). Stress hormones not only stimulate and insure supply of glucose, but also increase CK activity during stress (Adelbert, 2000). Pretreatment of **3b** ($P < 0.05$), **3d** ($P < 0.001$), **3e** ($P < 0.05$), **3g** ($P < 0.001$), **5b** ($P < 0.001$), **5c** ($P < 0.001$), **5d** ($P < 0.001$), **5g** ($P < 0.001$), and PQ ($P < 0.001$) significantly normalized the increased plasma corticosterone levels when compared to AS group, whereas **3a** ($P < 0.05$), **3b** ($P < 0.001$), **3d** ($P < 0.001$), **3e** ($P < 0.001$), **3g** ($P < 0.001$), **5a** ($P < 0.001$), **5b** ($P < 0.001$), **5c** ($P < 0.05$), **5d** ($P < 0.001$), **5g** ($P < 0.001$), and PQ ($P < 0.001$) were found effective in normalizing AS-induced hyperglycemia (Table 1). Also, pretreatment of **3b** ($P < 0.01$), **3d** ($P < 0.01$), **3e** ($P < 0.001$), **3g** ($P < 0.01$), **5b** ($P < 0.001$), **5c** ($P < 0.001$), **5d** ($P < 0.001$), **5g** ($P < 0.001$), and PQ ($P < 0.001$) significantly normalized the decreased CK activity when compared to AS group.

Table 1 Effect of **3a–g**, **5a–g**, and **PQ** on AS-induced perturbations in adrenal hypertrophy, ulcer severity, plasma glucose, CK, and corticosterone levels

Groups (dose mg/kg body weight p.o.)	Adrenal gland weight (mg/100 g body weight)	Mean ulcer score	Glucose (mg/dl)	CK (IU/dl)	Corticosterone (ng/ml)
Non-stress control	6.87 ± 0.81	0.0 ± 0.0	81.50 ± 3.374	323.5 ± 15.72	244.5 ± 15.43
AS + vehicle	10.20 ± 0.69$^{@}$	21.67 ± 3.07$^{@}$	134.7 ± 4.68$^{@}$	1115.0 ± 29.43$^{@}$	465.7 ± 15.77$^{@}$
3a (40)	9.31 ± 0.45	13.33 ± 2.11	112.0 ± 8.22*	1004.0 ± 57.30	432.2 ± 18.70
3b (40)	7.01 ± 0.54***	8.33 ± 3.07*	107.2 ± 4.42***	766.71 ± 47.73**	364.2 ± 20.18*
3c (40)	9.63 ± 0.45	18.33 ± 1.667	122.0 ± 2.95	1092.0 ± 64.26	446.0 ± 27.18
3d (40)	7.82 ± 0.47**	6.66 ± 2.11**	93.00 ± 5.62***	729.7 ± 77.58**	275.5 ± 31.65***
3e (40)	8.01 ± 0.42*	8.33 ± 3.07*	80.50 ± 6.63***	664.3 ± 77.36***	354.8 ± 17.78*
3f (40)	9.82 ± 0.42	16.67 ± 2.11	127.0 ± 3.12	934.7 ± 75.78	429.8 ± 23.94
3g (40)	7.60 ± 0.28**	10.00 ± 2.58*	101.7 ± 5.16***	733.8 ± 83.05**	320.0 ± 15.49***
5a (40)	9.86 ± 0.35	11.67 ± 3.07	86.24 ± 3.71***	998.5 ± 33.84	417.2 ± 21.09
5b (40)	7.77 ± 0.38**	10.00 ± 2.59*	74.67 ± 5.68***	673.0 ± 60.36***	311.8 ± 18.60***
5c (40)	7.54 ± 0.23**	6.66 ± 3.33**	109.51 ± 11.01*	590.0 ± 82.55***	293.5 ± 25.02***
5d (40)	7.89 ± 0.32*	10.00 ± 2.58*	72.83 ± 6.29***	625.7 ± 79.46***	292.3 ± 34.60***
5e (40)	9.60 ± 0.40	25.00 ± 2.23	116.3 ± 7.87	994.5 ± 50.50	444.7 ± 11.91
5f (40)	10.58 ± 0.58	16.67 ± 2.10	125.0 ± 4.83	1074.0 ± 73.93	421.0 ± 20.96
5g (40)	7.23 ± 0.40***	10.00 ± 2.58*	78.17 ± 2.88***	603.7 ± 78.54***	282.5 ± 14.01***
PQ (100)	7.32 ± 0.25***	5.00 ± 2.23**	68.33 ± 4.19***	649.3 ± 101.3***	247.3 ± 15.27***

Results are represented as means ± SEM with $n = 6$ in each group

$^{@}$ $P < 0.001$ when compared to the NS group and * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ when compared to AS group. The stress group was compared with the NS control group and the drug-treated groups were compared with an AS group

Conclusion

In summary, we have synthesized a series of novel isoxazolines and evaluate their anti-stress potential in AS model. AS resulted in significant elevation in gastric ulceration adrenal hypertrophy, hyperglycemia, plasma CK activity, and corticosterone levels, which was significantly countered by pretreatment of isoxazolines **3d**, **3g**, **5b**, **5c**, **5d**, and **5g**. Thus, the protective effects of these compounds during AS condition might be due to the normalization of increased HPA axis response during an immediate threat condition such as acute immobilization stress. Hence, these compounds might have important therapeutic implications in stress-induced neuropathological conditions, and biological activity profiles of these compounds are worthy for further investigation to develop anti-stress drugs.

Experimental

General

Mps are uncorrected and were determined on Complab apparatus. IR spectra were recorded on Perkin–Elmer RX-1 spectrometer using either KBr pallets or neat. The FAB MS results were recorded using a beam of argon (208 eV) on a Jeol SX 102/DA-6000 mass spectrometer. ^{1}H NMR spectra were recorded at AVANCE DPX 200 spectrometer and ^{13}C NMR spectra at 50 MHz on the same spectrometer, and are quoted relative to $C_4H_{12}Si$ as internal reference. Elemental analyses were obtained in a Carlo-Erba-1108 CHN elemental analyzer. Thin-layer chromatography was run on precoated 60F254 (Merck, Darmstadt, Germany) plated. Detection of spots was done either by I_2 vapor and spraying with 1% ceric sulfate in 1 M H_2SO_4 or spraying with 10% methanolic sulfuric acid followed by heating at 110°C.

Synthesis of olefins **2c–g**

General procedure

The mixture of **2** (1 equiv) with methyl iodide, ethyl iodide, benzyl bromide, *N*-(2-chloroethyl) pyrrolidine hydrochloride, and *N*-(2-chloroethyl) piperidine hydrochloride (1.2 equiv) and K_2CO_3 (1.2 equiv) in dry acetone was refluxed with stirring for 3 h, respectively. After that acetone was evaporated, water was added and the mixture was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous sodium sulfate. The products were purified by column chromatography over silica gel.

*4-Allyl-1,2-dimethoxy-benzene (**2c**)*

Yield 95.0, viscous oil, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.80 (1H, dd, $J = 8.6$, 1.6 Hz, H-5), 6.72 (1H, d, $J = 8.6$ Hz, H-6), 6.70 (1H, d, $J = 1.6$ Hz, H-3), 5.94 (1H, m, H-8), 5.10 (1H, d, $J = 18.2$, 7.6 Hz, H-9a), 5.07 (1H, dd, $J = 18.2$ Hz, H-9b), 3.85 (6H, s, 2× OCH_3), 3.32 (2H, d, $J = 6.8$ Hz, H-7); FAB MS *m/z* 179 $[M+1]^+$.

*4-Allyl-1-ethoxy-2-methoxy-benzene (**2d**)*

Yield 89%, viscous oil, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.82 (1H, dd, $J = 8.6$ Hz, H-6), 6.69 (2H, d, $J = 8.6$ Hz, H-3,5), 5.94 (1H, m, H-8), 5.11-5.02 (2H, m, H-9a,9b), 4.86 (2H, q, $J = 7.0$ Hz, $O\underline{CH_2}CH_3$), 3.84 (3H, s, OCH_3), 3.32 (2H, d, $J = 6.6$ Hz, H-7), 1.44 (3H, t, $J = 7.0$ Hz, $OCH_2\underline{CH_3}$); FAB MS *m/z* 193 $[M+1]^+$.

*4-Allyl-1-benzyloxy-2-methoxy-benzene (**2e**)*

Yield 84.0%, viscous oil, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.44–7.23 (5H, m, Ar), 6.81 (1H, d, $J = 8.0$ Hz, H-6), 6.72 (1H, d, $J = 1.8$ Hz, H-3), 6.65 (1H, dd, $J = 8.0$, 1.8 Hz, H-5), 5.96 (1H, m, H-8), 5.11 (2H, s, $–CH_2–$Ar), 5.10–4.99 (2H, m, H-9a,9b), 3.86 (3H, s, OCH_3), 3.31 (2H, d, $J = 6.6$ Hz, H-7); FAB MS *m/z* 255 $[M+1]^+$.

*1-[2-(4-Allyl-2-methoxy-phenoxy)-ethyl]-pyrrolidine (**2f**)*

Yield 88.5%, brown viscous oil, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.83 (1H, d, $J = 8.6$ Hz, H-6), 6.69 (2H, brd, $J = 8.6$ Hz, H-3,5), 5.93 (1H, m, H-8), 5.11 (2H, m, H-9a,9b), 4.12 (2H, t, $J = 6.2$ Hz, OCH_2), 3.84 (3H, s, OCH_3), 3.32 (2H, d, $J = 6.6$ Hz, H-7), 2.93 (2H, t, $J = 6.2$ Hz, $OCH_2\underline{CH_2}N$), 2.60 (4H, m, $N(CH_2)_2–$), 1.78 (4H, m, 2× CH_2); FAB MS *m/z* (+ve) 262 $[M+1]^+$. Elemental anal. calc. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36%; found C, 73.59; H, 8.39; N, 5.43.

*1-[2-(4-Allyl-2-methoxy-phenoxy)-ethyl]-piperidine (**2g**)*

Yield 90.7%, brown viscous oil, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.82 (1H, d, $J = 8.6$ Hz, H-6), 6.70 (2H, brd, $J = 8.5$ Hz, H-3,5), 5.96 (1H, m, H-8), 5.10 (2H, m, H-9a,9b), 4.11 (2H, t, $J = 6.4$ Hz, OCH_2), 3.82 (3H, s, OCH_3), 3.32 (2H, d, $J = 6.8$ Hz, H-7), 2.79 (2H, t, $J = 6.4$ Hz, $OCH_2\underline{CH_2}N$), 2.52 (4H, m, $N(CH_2)_2–$), 1.62 (6H, m, 3× CH_2); FAB MS *m/z* 276 $[M+1]^+$. Elemental anal. calc. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09%; found C, 74.17; H, 9.19; N, 5.14%.

Synthesis of isoxazolines **3a–g** and **5a–g**

General procedure

A mixture of oxime (1.1 equiv), chloramines-T·$3H_2O$ (1.1 equiv) and olefin (1.0 equiv) in ethanol (50 ml) were refluxed for 3 h. The progress of reaction was monitored by TLC. After completion of the reaction, the solvent was removed using rotavapor. The residue was dissolved in ether, washed with 1 N NaOH solution (3× 15 ml), water (25 ml), and saturated solution of NaCl, dried over anhydrous sodium sulfate. The solvent was evaporated and the cycloadduct was purified by column chromatography over silica gel.

*4-[3-(2,4-Dimethoxy-phenyl)-4,5-dihydro-isoxazol-5-ylmethyl]-2-methoxy-phenol (**3a**)*

Yield 78.9%, brown sticky solid; IR ($CHCl_3$) ν_{max}: 3285, 2947, 1607, 1528, 1353, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.58 (1H, d, $J = 8.4$ Hz, H-6′), 6.85 (1H, d, $J = 8.0$ Hz, H-6), 6.81 (1H, d, $J = 1.8$ Hz, H-3), 6.72 (1H, dd, $J = 8.0$, 1.8 Hz, H-5), 6.57 (1H, d, $J = 2.4$ Hz, H-3′), 6.50 (1H, dd, $J = 8.6$, 2.2 Hz, H-5′), 5.60 (1H, brs, OH), 4.86 (1H, m, H-8), 3.84 (9H, brs, 3× OCH_3), 3.41 (1H, dd, $J = 18.1$, 10.2 Hz, H-9a), 3.13 (1H, dd, $J = 18.1$, 7.6 Hz, H-9b), 3.01 (1H, dd, $J = 13.8$, 9.7 Hz, H-7a), 2.94 (1H, dd, $J = 13.8$, 6.6 Hz, H-7b); FABMS (+ve): *m/z* 344 $[M+1]^+$. Elemental anal. calc. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08; found C, 66.50; H, 6.12; N, 4.13%.

*4-[3-(2,4-dimethoxy-phenyl)-4,5-dihydro-isoxazol-5-ylmethyl]-2-methoxy-phenyl acetate (**3b**)*

Yield 81.9%, white solid, mp 117–118°C. IR (KBr) ν_{max}: 2930, 1762, 1683, 1511, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.61 (1H, d, $J = 8.4$ Hz, H-6′), 6.96 (1H, d, $J = 8.0$ Hz, H-6), 6.91 (1H, d, $J = 1.4$ Hz, H-3), 6.81 (1H, dd, $J = 8.0$, 1.8 Hz, H-5), 6.52 (1H, d, $J = 2.2$ Hz, H-3′), 6.47 (1H, dd, $J = 8.2$, 1.8 Hz, H-5′), 4.87 (1H, m, H-8), 3.83 (9H, brs, 3× OCH_3), 3.49 (1H, dd, $J = 17.2$, 11.0 Hz, H-9a), 3.15 (1H, dd, $J = 17.2$, 7.6 Hz, H-9b), 3.08 (1H, dd, $J = 13.8$, 9.2 Hz, H-7a), 2.83 (1H, dd, $J = 14.2$, 6.6 Hz, H-7b), 2.29 (3H, s, $OCOCH_3$); FAB MS (+ve): *m/z* 385 $[M+1]^+$. Elemental anal. calc. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63; found C, 65.48; H, 6.07; N, 3.58%.

*5-(3,4-Dimethoxy-benzyl)-3-(2,4-dimethoxy-phenyl)-4,5-dihydro-isoxazole (**3c**)*

Yield 82.0%, white needle-shaped crystals, mp 98–99°C. IR (KBr) ν_{max}: 2938, 1597, 1515, 1351, 1157 cm^{-1}; ^{1}H

NMR ($CDCl_3$, 200 MHz) δ 7.80 (1H, d, $J = 8.2$ Hz, H-6′), 7.59 (1H, d, $J = 8.4$ Hz, H-6), 7.29 (2H, d, $J = 8.8$ Hz, H-3,5), 6.80 (1H, d, $J = 2.2$ Hz, H-3′), 6.49 (1H, dd, $J = 8.4$, 2.4 Hz, H-5′), 4.87 (1H, m, H-8), 3.87 (12H, brs, 4× OCH_3), 3.41 (1H, dd, $J = 17.2$, 10.0 Hz, H-9a), 3.12 (1H, dd, $J = 17.2$, 7.6 Hz, H-9b), 3.04 (1H, dd, $J = 13.4$, 6.2 Hz, H-7a), 2.80 (1H, dd, $J = 13.8$, 6.6 Hz, H-7b); FAB MS (+ve): *m/z* 357 [M^+], 358 [$M+1]^+$. Elemental anal: calc. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; found C, 67.25; H, 6.54; N, 3.98%.

*3-(2,4-Dimethoxy-phenyl)-5-(4-ethoxy-3-methoxy-benzyl)-4,5-dihydro-isoxazole (**3d**)*

Yield 75.6%, white solid, mp 92–93°C. IR (KBr) ν_{max}: 3021, 2361, 1769, 1628, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.76 (1H, d, $J = 8.2$ Hz, H-6′), 7.58 (1H, d, $J = 8.4$ Hz, H-6), 7.34 (1H, s, H-3), 6.79 (2H, dd, $J = 8.2$, 1.5 Hz, H-3′,5), 6.47 (1H, dd, $J = 8.4$, 2.4 Hz, H-5′), 4.86 (1H, m, H-8), 4.06 (2H, q, $J = 7.0$ Hz, $O\underline{CH_2}CH_3$), 3.82 (9H, brs, 3× OCH_3), 3.33 (1H, dd, $J = 18.1$, 10.0 Hz, H-9a), 3.12 (1H, dd, $J = 18.1$, 7.4 Hz, H-9b), 3.01 (1H, dd, $J = 13.1$, 6.6 Hz, H-7a), 2.98 (1H, dd, $J = 13.1$, 6.6 Hz, H-7b), 1.43 (3H, t, $J = 7.0$ Hz, $OCH_2\underline{CH_3}$); FAB MS (+ve): *m/z* 372 [M^+]. Elemental anal: calc. for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77; found C, 67.84; H, 6.71; N, 3.72%.

*5-(4-Benzyloxy-3-methoxy-benzyl)-3-(2,4-dimethoxy-phenyl)-4,5-dihydro-isoxazole (**3e**)*

Yield 81.0%, white crystals, mp 83–84°C. IR (KBr) ν_{max}: 3021, 1616, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.60(1H, d, $J = 8.4$ Hz, H-6′), 7.45–7.23 (5H, m, H-2″ to 6″), 6.84 (1H, d, $J = 1.8$ Hz, H-3), 6.81 (1H, d, $J = 8.2$ Hz, H-6), 6.70 (1H, d, $J = 8.2$, 1.8 Hz, H-5), 6.51 (1H, d, $J = 2.4$ Hz, H-3′), 6.46 (1H, dd, $J = 7.0$, 2.4 Hz, H-5′), 5.13 (2H, s, CH_2Ar), 4.87 (1H, m, H-8), 3.88 (9H, brs, 3× OCH_3), 3.40 (1H, dd, $J = 17.2$, 10.0 Hz, H-9a), 3.13 (1H, dd, $J = 17.2$, 7.6 Hz, H-9b), 3.03 (1H, dd, $J = 13.8$, 6.8 Hz, H-7a), 2.81 1H, dd, $J = 13.8$, 6.6 Hz, H-7b); FAB MS (+ve): *m/z* 434 [$M+1]^+$. Elemental anal. calc. for $C_{26}H_{27}NO_5$: C, 72.04; H, 6.28; N, 3.23; found C, 72.12; H, 6.31; N, 3.16%.

*3-(2,4-Dimethoxy-phenyl)-5-[3-methoxy-4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-4,5-dihydro-isoxazole (**3f**)*

Yield 73.9%, brown viscous oil. IR (neat) ν_{max}: 3020, 1613, 1513, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.39(1H, d, $J = 8.4$ Hz, H-6′), 6.62 (1H, d, $J = 7.4$ Hz, H-6), 6.56 (2H, m, H-3,5), 6.30 (1H, d, $J = 2.2$ Hz, H-3′), 6.27 (1H, dd, $J = 8.3$, 1.7 Hz, H-5′), 4.72 (1H, m, H-8), 3.95 (2H, t, $J = 6.2$ Hz, OCH_2), 3.85 (3H, brs, OCH_3), 3.84 (3H, brs, OCH_3), 3.82 (3H, brs, OCH_3), 3.39 (1H, dd, $J = 17.1$, 10.4 Hz, H-9a), 3.14 (1H, dd, $J = 17.1$, 10.0 Hz, H-9b), 3.09 (1H, dd, $J = 14.1$, 6.8 Hz, H-7a), 2.87 (1H, dd, $J = 14.1$, 6.2 Hz, H-7b), 2.85 (2H, t, $J = 6.2$ Hz, –CH_2–N), 2.60 (4H, m, –$N(CH_2)_2$–), 1.79 (4H, m, –CH_2CH_2–); FAB MS (+ve): *m/z* 441 [$M+1]^+$. Elemental anal. calc. for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36; found C, 68.07; H, 7.40; N, 6.40%.

*1-(2-{4-[3-(2,4-Dimethoxy-phenyl)-4,5-dihydro-isoxazol-5-ylmethyl]-2-methoxy-phenoxy}-ethyl)-piperidine (**3g**)*

Yield 80.9%, brown viscous oil. IR (neat) ν_{max}: 3019, 1609, 1350, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.60(1H, d, $J = 8.4$ Hz, H-6′), 6.83 (1H, d, $J = 7.6$ Hz, H-6), 6.81 (2H, m, H-3,5), 6.49 (1H, dd, $J = 8.0$, 1.8 Hz, H-5′), 4.86 (1H, m, H-8), 6.52 (1H, d, $J = 1.8$ Hz, H-3′), 4.13 (2H, t, $J = 6.2$ Hz, OCH_2), 3.85 (3H, brs, OCH_3), 3.84 (3H, brs, OCH_3), 3.82 (3H, brs, OCH_3), 3.39 (1H, dd, $J = 17.2$, 10.0 Hz, H-9a), 3.14 (1H, dd, $J = 17.2$, 10.0 Hz, H-9b), 3.09 (1H, dd, $J = 14.2$, 6.2 Hz, H-7a), 2.87 (1H, dd, $J = 14.2$, 6.8 Hz, H-7b), 2.84 (2H, t, $J = 6.0$ Hz, –CH_2–N), 2.58 (4H, m, –$N(CH_2)_2$–), 1.66 (6H, m, –$CH_2CH_2CH_2$–); FAB MS (+ve): *m/z* 455 [$M+1]^+$. Elemental anal. calc. for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16; found C, 68.73; H, 7.48; N, 6.10%.

*2-Methoxy-4-(3-naphthalen-1-yl-4,5-dihydro-isoxazol-5-ylmethyl)-phenol (**5a**)*

Yield 88.0%, sticky solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.80 (1H, d, $J = 7.3$ Hz, H-8′), 7.80 (2H, m, H-2′,4′), 7.58 (4H, m, H-3′,5′,6′,7′), 6.80 (3H, m, H-3,5,6), 5.00 (1H, m, H-8), 3.89 (3H, brs, OCH_3), 3.56 (1H, dd, $J = 16.1$, 10.3 Hz, H-9a), 3.27 (1H, dd, $J = 16.1$, 7.7 Hz, H-9b), 3.08 (1H, dd, $J = 14.5$, 7.8 Hz, H-7a), 2.97 (1H, dd, $J = 14.5$, 6.4 Hz, H-7b); FAB MS (+ve): *m/z* 333 [$M]^+$, 334 [$M+1]^+$. Elemental anal. calc. for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20; found C, 75.58; H, 5.70; N, 4.13%.

*2-Methoxy-4-(3-naphthalen-1-yl-4,5-dihydro-isoxazol-5-ylmethyl)-phenyl acetate (**5b**)*

Yield 85.0%, brown sticky solid. IR (KBr) ν_{max}: 3021, 2361, 1601, 1514, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.88 (1H, d, $J = 7.6$ Hz, H-8′), 7.78 (2H, m, H-2′,4′), 7.58 (4H, m, H-3′,5′,6′,7′), 6.98 (1H, d, $J = 8.1$ Hz, H-6), 6.95 (1H, d, $J = 1.2$ Hz, H-3), 6.81 (1H, dd, $J = 8.1$, 1.2 Hz, H-5), 5.02 (1H, m, H-8), 3.87 (3H, brs, OCH_3), 3.54 (1H, dd, $J = 16.6$, 10.2 Hz, H-9a), 3.26 (1H, dd, $J = 16.6$, 7.8 Hz, H-9b), 3.17 (1H, dd, $J = 13.2$, 6.2 Hz, H-7a), 2.95 (1H, dd, $J = 13.2$, 5.2 Hz, H-7b), 2.45

(3H, s, $COCH_3$); FAB MS (+ve): *m/z* 376 $[M+1]^+$. Elemental anal. calc. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73; found C, 73.66; H, 6.01; N, 3.65%.

*5-(3,4-Dimethoxy-benzyl)-3-(naphthalen-1-yl)-4,5-dihydroisoxazole (**5c**)*

Yield 87.1%, white needle-shaped crystals, mp 103–104°C. IR (KBr) ν_{max}: 2938, 1592, 1235, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.84 (1H, dd, $J = 7.4$, 2.0 Hz, H-8′), 7.88 (2H, m, H-2′,4′), 7.56 (4H, m, H-3′,5′,6′,7′), 6.84 (3H, m, H-3,5,6), 5.01 (1H, m, H-8), 3.88 (3H, brs, OCH_3), 3.85 (3H, brs, OCH_3), 3.53 (1H, dd, $J = 16.6$, 10.2 Hz, H-9a), 3.24 (1H, dd, $J = 16.6$, 7.6 Hz, H-9b), 3.12 (1H, dd, $J = 14.2$, 8.0 Hz, H-7a), 2.94 (1H, dd, $J = 14.2$, 6.4 Hz, H-7b); FAB MS (+ve): *m/z* 348 $[M+1]^+$. Elemental anal. calc. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03; found C, 76.00; H, 6.01; N, 4.11%.

*5-(4-Ethoxy-3-methoxy-benzyl)-3-naphthalen-1-yl-4,5-dihydro-isoxazole (**5d**)*

Yield 77.4%, brown sticky solid. IR (KBr) ν_{max}: 3377, 1596, 1514, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.86 (1H, dd, $J = 7.6$, 1.8 Hz, H-8′), 7.87 (2H, m, H-2′,4′), 7.61 (4H, m, H-3′,5′,6′,7′), 6.85 (3H, m, H-3,5,6), 4.99 (1H, m, H-8), 4.06 (2H, q, $J = 7.0$ Hz, $O\underline{CH_2}CH_3$)), 3.87 (3H, brs, OCH_3), 3.52 (1H, dd, $J = 16.6$, 10.2 Hz, H-9a), 3.23 (1H, dd, $J = 16.6$, 7.8 Hz, H-9b), 3.14 (1H, dd, $J = 15.8$, 7.8 Hz, H-7a), 2.93 (1H, dd, $J = 15.8$, 6.6 Hz, H-7b); ESI MS *m/z* 361 $[M+1]^+$. Elemental anal. calc. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88; found C, 76.35; H, 6.49; N, 3.79%.

*5-(4-Benzyloxy-3-methoxy-benzyl)-3-naphthalen-1-yl-4,5-dihydro-isoxazole (**5e**)*

Yield 72.8%, white crystals, mp 104–105°C. IR (KBr) ν_{max}: 2930, 1593, 1236, 1147 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.86 (1H, dd, $J = 7.6$, 1.8 Hz, H-8′), 7.88 (2H, m, H-2′,4′), 7.58-7.30 (9H, m, H-3′,5′,6′,7′, 2″–6″), 6.88 (1H, d, $J = 1.8$ Hz, H-3), 6.82 (1H, d, $J = 8.0$ Hz, H-6), 6.74 (1H, dd, $J = 8.0$, 1.8 Hz, H-5), 5.11 (2H, s, –$\underline{CH_2}$Ar), 5.01 (1H, m, H-8), 3.89 (3H, brs, OCH_3), 3.55 (1H, dd, $J = 14.8$, 10.2 Hz, H-9a), 3.22 (1H, dd, $J = 14.8$, 7.6 Hz, H-9b), 3.12 (1H, dd, $J = 14.0$, 5.8 Hz, H-7a), 2.92 (1H, dd, $J = 14.0$, 6.2 Hz, H-7b); ESI MS *m/z* 423 $[M]^+$, 424 $[M+1]^+$. Elemental anal. calc. for $C_{28}H_{25}NO_3$: C, 79.41; H, 5.95; N, 3.31; found C, 79.51; H, 6.00; N, 6.30%.

*5-[3-Methoxy-4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-3-naphthalen-1-yl-4,5-dihydro-isoxazole (**5f**)*

Yield 78.6%, brown solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.87 (1H, dd, $J = 9.1$, 1.7 Hz, H-8′), 7.91 (2H, m, H-2′,4′), 7.59-7.40 (4H, m, H-3′,5′,6′,7′), 6.98 (1H, d, $J = 1.8$ Hz, H-3), 6.80 (1H, dd, $J = 8.0$, 1.8 Hz, H-5), 6.70 (1H, d, $J = 8.0$ Hz, H-6), 5.04 (1H, m, H-8), 4.16 (2H, t, $J = 5.8$ Hz, $–OCH_2$), 3.88 (3H, brs, OCH_3), 3.65 (1H, dd, $J = 15.1$, 9.5 Hz, H-9a), 3.32 (1H, dd, $J = 15.1$, 6.5 Hz, H-9b), 3.02 (1H, dd, $J = 14.0$, 6.5 Hz, H-7a), 2.81 (1H, dd, $J = 14.0$, 6.2 Hz, H-7b), 2.82 (2H,t, $J = 6.0$ Hz $–NCH_2$), 2.64 (4H, m, $H–N(CH_2)_2–$), 1.72 (4H, m, $–CH_2CH_2–$); FABMS *m/z* 431 $[M+1]^+$. Elemental anal. calc. for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51; found C, 75.41; H, 7.11; N, 6.42%.

*1-{2-[2-Methoxy-4-(3-naphthalen-1-yl-4,5-dihydro-isoxazol-5-ylmethyl)-phenoxy]-ethyl}-piperidine (**5g**)*

Yield 88.6%, brown sticky solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.85 (1H, dd, $J = 9.2$, 1.8 Hz, H-8′), 7.94 (2H, m, H-2′,4′), 7.60-7.43 (4H, m, H-3′,5′,6′,7′), 6.96 (1H, d, $J = 2.1$ Hz, H-3), 6.82 (1H, dd, $J = 8.2$, 2.1 Hz, H-5), 6.69 (1H, d, $J = 8.2$ Hz, H-6), 5.03 (1H, m, H-8), 4.18 (2H, t, $J = 5.8$ Hz, $–OCH_2$), 3.85 (3H, brs, OCH_3), 3.61 (1H, dd, $J = 15.6$, 9.8 Hz, H-9a), 3.30 (1H, dd, $J = 15.6$, 6.8 Hz, H-9b), 3.25–3.06 (2H, m, H-7ab), 3.00 (2H,brs, $–NCH_2$), 2.70 (4H, m, $H–N(CH_2)_2–$), 1.71–1.65 (6H, m, $H–CH_2CH_2CH_2–$); FAB MS *m/z* 444 $[M]^+$, 445 $[M+1]^+$. Elemental anal. calc. for $C_{28}H_{32}N_2O_3$: C, 75.65; H, 7.26; N, 6.30; found C, 75.57; H, 7.1; N, 6.37%.

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