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ORIGINAL ARTICLE

Synthesis and goat pulmonary vasodilatory activity of some novel 1,3,4-oxadiazoles

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KEYWORDS

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Abstract A novel series of [(1*Z*)-1-(2,2-disubstituted-5-pyridin-4-yl-1,3,4-oxadiazol-3(*2H*)-yl) ethylidene] (**PSMB1**–**PSMB15**) were synthesized as title compounds. The synthesis route included the cyclization of carbonyl hydrazone in the presence of excess of acetic anhydride and subsequent condensation with various aromatic amines. All the title compounds were characterized by IR, ^{1}H NMR, MS and elemental analysis. They were screened for their goat pulmonary vein relaxant activity. Compound **PSMB9** was found the most active derivative exhibiting 83.33% relaxation. Isosorbide dinitrate was used as the standard drug for goat pulmonary vein relaxant activity.

1. Introduction

Research on 1,3,4-oxadiazole skeleton derivatives has attracted sizeable interest because of their assorted biological activity, including anti-HIV activity, (Taoa et al., 2006), antibacterial (Sahin and Palaska, 2002; Ates et al., 1998; Kocabalkanli et al., 2001), antifungal, analgesic and anti-inflammatory activities (Palaska et al., 2002; Mishrah et al., 1995; Maccari et al., 2005; Demirbas, 2005) and, smooth muscle relaxant (Ahulwalia et al., 1989; Dhiman et al., 2001). Moreover, they are also effective in conjunction with imines and nitric oxide and display diverse potent physiological actions (Sad, 1996; Ram, 1988; Misra et al., 1996; Shah et al., 1998; Amir and Kumar, 2004). With regard to the cardiovascular system, it helps to maintain micro- and macro-vascular homeostasis through several mechanisms including vasodilatation, inhibition of platelet aggregation, and modulation of platelet and leukocyte adhesion to the endothelium (Mogilaiah and Sakram, 2004; Gasco et al., 2004). Based on the fact, it is envisioned that the attachment of imines to the 1,3,4-oxadiazole can enhance the pulmonary vein relaxation which may contribute to maintain the homeostasis and in continuation of our research on synthesis of pharmacological active oxadiazole and imines, herein we report the synthesis of a novel series of 5-(pyridyl)-1,3,4-oxadiazole. All the title compounds were evaluated for goat pulmonary vein relaxation (Chand, 1981; Chand et al., 1979) using force transducer multichannel physiograph (BIOPAC MP35 SYSTEM). The synthesis route is outlined in Fig. 1.

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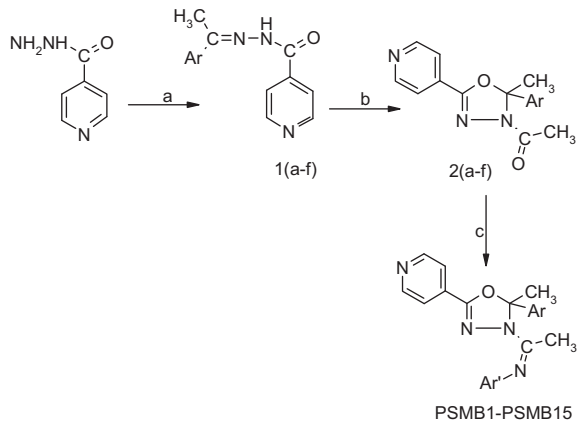


Figure 1 Synthesis route of compounds **PSMB1**–**PSMB15**. Key: (a) acetophenones–methanol; (b) acetic anhydride; (c) aromatic amines.

2. Experimental

2.1. General

Melting points were determined by open capillary method and were uncorrected. IR spectra (KBr wafer technique) were recorded on a Nicolet Impact-410 FT (Nicolet Instrumentation Corporation, Madison, WI, USA), ^{1}H NMR spectra were recorded in $CDCl_3$ on a Brucker 300 MHz (Brucker Magnetics AG, Faellanden, Switzerland) using TMS as the internal standard. Mass spectra were obtained with a HPLC/MS LCQ-DECA spectrometer. HRMS-FAB was obtained with Mass Spectrometers JoelSX-102. Elemental analysis was performed on a Perkin–Elmer model 240C analyzer and the data were within ±0.4% of the theoretical values. The purity of the compounds was confirmed by TLC on silica gel 'G' (60-120 mesh size) coated glass plates.

*2.1.1. Typical procedure for synthesis of (2E)-2-[(Z)-2-aminovinyl]-N′-[1-(aryl)ethylidene]penta-2,4-dienehydrazide **1(a–f)***

A solution of 0.01 mol of isoniazid and an equimolar amount of appropriate acetophenones were added in 25 ml methanol with a drop of glacial acetic acid, consecutively; the reaction mixture was refluxed for about 2 h until the disappearance of the starting material which was ascertained by TLC. The precipitate obtained was filtered-off; washed with cold methanol and was then recrystallized from methanol to give **1(a–f)**. Analytical and spectral data was obtained for all the compounds.

*2.1.2. (2E)-2-[(Z)-2-aminovinyl]-N′-[1-(phenyl)ethylidene] penta-2,4-dienehydrazide **1(a)***

Yield 84%; m.p. 187–188 °C; IR (KBr) V_{max}/cm^{-1}: 3280 (N–H), 3010 (Ar, C–H), 1685 (C═O), 1589 (C═C), 1575 (C═N); ^{1}H NMR ($CDCl_3$) δ: 2.37 (s, 3H, CH_3), 5.23 (s, 1H, NH), 7.2–7.62 (m, 5H, aromatic). 7.65–8.43 (m, 4H, pyridinyl).

*2.1.3. (2E)-2-[(Z)-2-aminovinyl]-N′-[1-(4-chlorophenyl)-ethylidene]penta-2,4-dienehydrazide **1(b)***

Yield 79%; m.p. 205–206 °C; IR (KBr) V_{max}/cm^{-1}: 3295 (N–H), 2980 (Ar, C–H), 1684 (C═O), 1589 (C═C), 1579 (C═N), 670 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 2.33 (s, 3H, CH_3), 5.30 (s, 1H, NH), 6.92–7.42 (m, 4H, aromatic). 7.63–8.45 (m, 4H, pyridinyl).

*2.1.4. (2E)-2-[(Z)-2-aminovinyl]-N′-[1-(4-bromophenyl)-ethylidene]penta-2,4-dienehydrazide **1(c)***

Yield 86%; m.p. 207–208 °C; IR (KBr) V_{max}/cm^{-1}: 3290 (N–H), 2985 (Ar, C–H), 1690 (C═O), 1595 (C═C), 1576 (C═N), 430 (C–Br).

*2.1.5. (2E)-2-[(Z)-2-aminovinyl]-N′-[1-(4-methoxyphenyl)-ethylidene]penta-2,4-dienehydrazide **1(d)***

Yield 76%; m.p. 195–196 °C; IR (KBr) V_{max}/cm^{-1}: 3293 (N–H), 2988 (Ar, C–H), 1693 (C═O), 1610 (C═C), 1587 (C═N); ^{1}H NMR ($CDCl_3$) δ: 3.67 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3), 5.34 (s, 1H, NH), 7.2–7.42 (m, 4H, aromatic). 7.58–8.33 (m, 4H, pyridinyl).

*2.1.6. (2E)-2-[(Z)-2-aminovinyl]-N′-[1-(4-nitrophenyl)-ethylidene]penta-2,4-dienehydrazide **1(e)***

Yield 83%; m.p. 209–210 °C; IR (KBr) V_{max}/cm^{-1}: 3320 (N–H), 2994 (Ar, C–H), 1688 (C═O), 1609 (C═C), 1578 (C═N), 1510 (N═O); ^{1}H NMR ($CDCl_3$) δ: 2.38 (s, 3H, CH_3), 5.28 (s, 1H, NH), 7.34–7.62 (m, 4H, aromatic). 7.52–8.3 (m, 4H, pyridinyl).

*2.1.7. (2E)-2-[(Z)-2-aminovinyl]-N′-[1-(3-nitrophenyl)-ethylidene]penta-2,4-dienehydrazide **1(f)***

Yield 80%; m.p. 207–208 °C; IR (KBr) V_{max}/cm^{-1}: 3335 (N–H), 2998 (Ar, C–H), 1689 (C═O), 1610 (C═C), 1588 (C═N), 1505 (N═O).

*2.1.8. Typical procedure for synthesis of 1-acetamido-1-(Aryl) ethyl(1Z,2E,3Z)-2-(2-imino ethylidene)-N-methylpent-3-enimidoate **2(a–f)***

A mixture of 0.01 mol of the appropriate compound **1(a–f)** and an excess of acetic anhydride was refluxed for 2 h until the completion of the reaction which was monitored by TLC. Excess of acetic anhydride was distilled off and the residue was poured onto crushed ice. The solid thus obtained was filtered; washed with water and was then recrystallized with aqueous methanol to obtain **2(a–f)**. Analytical and spectral data was obtained for all the compounds.

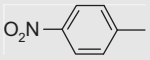
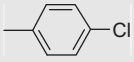
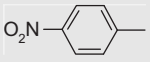
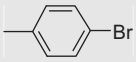
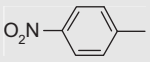
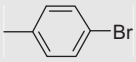
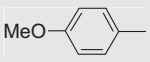
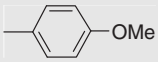
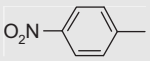
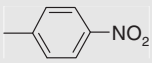
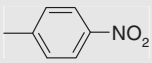
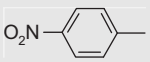
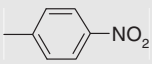
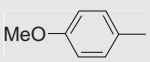
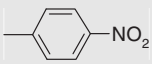
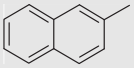
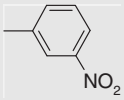
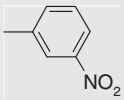
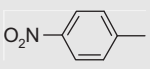
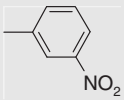
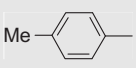
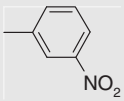
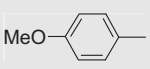
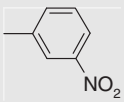
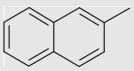
*2.1.9. 1-Acetamido-1-(phenyl) ethyl(1Z,2E,3Z)-2-(2-iminoethylidene)-N-methylpent-3-enimidoate **2(a)***

Yield 78%; m.p. 154–155 °C; IR (KBr) V_{max}/cm^{-1}: 2995 (Ar, C–H), 1695 (C═O), 1587 (C═C), 1595 (C═N, oxadiazolyl), 1586 (C═N, pyridinyl); ^{1}H NMR ($CDCl_3$) δ: 2.32 (s, 3H, CH_3), 2.18 (s, 3H, $COCH_3$), 6.9–7.58 (m, 5H, aromatic). 7.62–8.23 (m, 4H, pyridinyl).

*2.1.10. 1-Acetamido-1-(4-chlorophenyl) ethyl(1Z,2E,3Z)-2-(2-iminoethylidene)-N-methylpent-3-enimidoate **2(b)***

Yield 87%; m.p. 162–163 °C; IR (KBr) V_{max}/cm^{-1}: 2983 (Ar, C–H), 1689 (C═O), 1588 (C═C), 1592 (C═N, oxadiazolyl), 157 (C═N), 655 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 2.31 (s, 3H, CH_3), 2.09 (s, 3H, $COCH_3$), 6.91–7.32 (m, 4H, aromatic). 7.58–8.35 (m, 4H, pyridinyl).

Table 1 Physical properties of **PSMB1**–**PSMB15**.

Compound	Ar	Ar[1]	Molecular formula	Molecular weight	Color	Yield (%)
PSMB1			$C_{22}H_{20}N_4O$	356.43	Light yellow	68
PSMB2			$C_{22}H_{19}N_5O_3$	401.43	Yellow	69
PSMB3			$C_{22}H_{18}ClN_5O_3$	435.87	Light brown	72
PSMB4			$C_{22}H_{18}BrN_5O_3$	480.32	Dark yellow	73
PSMB5			$C_{23}H_{21}BrN_4O_2$	465.35	Light yellow	65
PSMB6			$C_{23}H_{21}N_5O_4$	431.45	Yellowish brown	68
PSMB7			$C_{22}H_{19}N_5O_3$	401.43	Light brown	72
PSMB8			$C_{22}H_{18}N_6O_5$	446.43	Yellow	70
PSMB9			$C_{23}H_{21}N_5O_4$	431.45	Brown	67
PSMB10			$C_{26}H_{21}N_5O_3$	451.49	Yellowish -white	68
PSMB11			$C_{22}H_{19}N_5O_3$	401.43	Light brown	69
PSMB12			$C_{22}H_{18}N_6O_5$	446.43	Dark-yellow	73
PSMB13			$C_{23}H_{21}N_5O_3$	415.46	Brown	70
PSMB14			$C_{23}H_{21}N_5O_4$	431.45	Brown	63
PSMB15			$C_{26}H_{21}N_5O_3$	451.49	Yellowish -white	64

*2.1.11. 1-Acetamido-1-(4-bromophenyl) ethyl(1Z,2E,3Z)-2-(2-iminoethylidene)-N-methylpent-3-enimidoate **2(c)***

Yield 78%; m.p. 175–176 °C; IR (KBr) V_{max}/cm^{-1}: 2984 (Ar, C–H), 1690 (C═O), 1586 (C═C), 1593 (C═N, oxadiazolyl), 1576 (C═N), 465 (C–Br).

*2.1.12. 1-Acetamido-1-(4-methoxyphenyl)ethyl(1Z,2E,3Z)-2-(2-iminoethylidene)-N-methylpent-3-enimidoate **2(d)***

Yield 78%; m.p. 165–166 °C; IR (KBr) V_{max}/cm^{-1}: 2986 (Ar, C–H), 1698 (C═O), 1589 (C═C), 1598 (C═N, oxadiazolyl), 1587 (C═N); ^1H NMR ($CDCl_3$) δ: 3.65 (s, 3H, $-OCH_3$),

2.39 (s, 3H, CH_3), 2.09 (s, 3H, $COCH_3$), 6.98–7.27 (m, 4H, aromatic). 7.38–7.98 (m, 4H, pyridinyl).

*2.1.13. 1-Acetamido-1-(4-nitrophenyl)ethyl(1Z,2E,3Z)-2-(2-iminoethylidene)-N-methylpent-3-enimidoate **2(e)***
Yield 78%; m.p. 123–124 °C; IR (KBr) V_{max}/cm^{-1}: 2984 (Ar, C–H), 1689 (C═O), 1580 (C═C), 1594 (C═N, oxadiazolyl), 1578 (C═N), 1508 (N═O); ^1H NMR ($CDCl_3$) δ: 2.32 (s, 3H, CH_3), 2.07 (s, 3H, $COCH_3$), 7.44–7.67 (m, 4H, aromatic). 7.72–8.14 (m, 4H, pyridinyl).

*2.1.14. 1-Acetamido-1-(3-nitrophenyl)ethyl(1Z,2E,3Z)-2-(2-iminoethylidene)-N-methylpent-3-enimidoate **2(f)***
Yield 78%; m.p. 128–129 °C; IR (KBr) V_{max}/cm^{-1}: 2983 (Ar, C–H), 1688 (C═O), 1584 (C═C), 1593 (C═N, oxadiazolyl), 1575 (C═N), 1510 (N═O).

*2.1.15. General procedure for synthesis of N-{(1Z)-1-[2-methyl-2-(aryl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-aromatic amines (**PSMB1–PSMB15**)*
A mixture of 0.01 mol of **2(a–f)** and an equimolar amount of appropriate aromatic amines was added to 25 ml ethanol with a drop of glacial acetic acid, was heated under reflux for 5–6 h. The precipitate obtained was filtered-off; washed with cold ethanol and recrystallized from ethanol to give **PSMB1–PSMB15**. Physical properties are given in Table 1 and Analytical and spectral data were obtained from all the compounds.

*2.1.16. N-[(1Z)-1-(2-methyl-2-phenyl-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl)ethylidene]aniline (**PSMB1**)*
Yield 68%, m.p. 205–206 °C; found: C, 73.85; H, 5.10; N, 15.65. Calc. for $C_{22}H_{20}N_4O$ (356.43): C, 74.14; H, 5.66; N, 15.72; IR (KBr) V_{max}/cm^{-1}: 2983 (Ar, C–H), 1584 (C═C), 1593 (C═N, oxadiazolyl), 1575 (C═N); ^1H NMR ($CDCl_3$) δ: 2.30 (s, 3H, CH_3), 2.02 (s, 3H, N═C–CH_3), 7.2–7.38 (m, 10H, aromatic), 7.45–8.10 (m, 4H, pyridinyl); MS (*m*/*z*): 357 (M + 1), 358 (M + 2).

*2.1.17. N-[(1Z)-1-(2-methyl-2-phenyl-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl)ethylidene]-4-nitroaniline (**PSMB2**)*
Yield 69%, m.p. 210–211 °C; found: C, 64.83; H, 4.85; N, 16.25. Calc. for $C_{22}H_{19}N_5O_3$ (401.43): C, 65.83; H, 4.77; N, 17.45; IR (KBr) V_{max}/cm^{-1}: 2985 (Ar, C–H), 1586 (C═C), 1595 (C═N, oxadiazolyl), 1510 (N═O), 1573 (C═N); ^1H NMR ($CDCl_3$) δ:2.31 (s, 3H, CH_3), 2.01 (s, 3H, N═C–CH_3), 7.1–7.23 (m, 9H, aromatic), 7.55–8.12 (m, 4H, pyridinyl); MS (*m*/*z*): 402 (M + 1), 403 (M + 2).

*2.1.18. N-{(1Z)-1-[2-(4-chlorophenyl)-2-methyl-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-4-nitroaniline (**PSMB3**)*
Yield 72%, m.p. 233–234 °C; found: C, 61.55; H, 4.10; N, 9.65. Calc. for $C_{22}H_{18}ClN_5O_3$ (435.87): C, 60.62; H, 4.16; N, 8.13; IR (KBr) V_{max}/cm^{-1}: 2963 (Ar, C–H), 1574 (C═C), 1599 (C═N, oxadiazolyl), 1517 (N═O), 1574 (C═N); ^1H NMR ($CDCl_3$) δ: 2.28 (s, 3H, CH_3), 2.03 (s, 3H, N═C–CH_3), 6.9–7.18 (m, 8H, aromatic). 7.15–8.0 (m, 4H, pyridinyl); MS (*m*/*z*): 437 (M + 1), 438 (M + 2) (HRMS calcd for $C_{22}H_{18}ClN_5O_3$ 435.8735, found 435.8741).

*2.1.19. N-{(1Z)-1-[2-(4-bromophenyl)-2-methyl-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-4-nitroaniline (**PSMB4**)*
Yield 73%, m.p. 236–237 °C; found:C, 54.85;H, 4.10; N, 14.65. Calc. for $C_{22}H_{18}BrN_5O_3$ (480.32): C, 55.01; H, 3.78; N, 14.58; IR (KBr) V_{max}/cm^{-1}: 2963 (Ar, C–H), 1578 (C═C), 1597 C═N, oxadiazolyl), 1516 (N═O), 1569 (C═N); ^1H NMR ($CDCl_3$) δ: 2.35 (s, 3H, CH_3), 2.10 (s, 3H, N═C–CH_3), 7.4–7.60 (m, 8H, aromatic). 7.65–8.10 (m, 4H, pyridinyl); MS (*m*/*z*): 481 (M + 1), 482 (M + 2) (HRMS calcd for $C_{22}H_{18}BrN_5O_3$ 480.3245, found 480.3250).

*2.1.20. N-{(1Z)-1-[2-(4-bromophenyl)-2-methyl-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-4-methoxyaniline (**PSMB5**)*
Yield 65%, m.p. 208–209 °C; found: C, 60.15; H, 4.45; N, 12.55. Calc. for $C_{23}H_{21}BrN_4O_2$ (465.35): C, 59.36; H, 4.55; N, 12.04; IR (KBr) V_{max}/cm^{-1}: 3010 (Ar, C–H), 1576 (C═C), 1591 (C═N, oxadiazolyl), 1572 (C═N); ^1H NMR ($CDCl_3$) δ: 2.30 (s, 3H, CH_3), 2.04 (s, 3H, N═C–CH_3), 3.70 (s, 3H, OCH_3), 7.1–7.40 (m, 8H, aromatic). 7.45–7.90 (m, 4H, pyridinyl); MS (*m*/*z*): 466 (M + 1), 467 (M + 2) (HRMS calcd for $C_{23}H_{21}BrN_4O_2$ 465.3534, found 465.3539).

*2.1.21. N-{(1Z)-1-[2-methyl-2-(4-methoxyphenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-4-nitroaniline (**PSMB6**)*
Yield 68%, m.p. 210–211 °C; found: C, 63.89; H, 4.95; N, 15.65. Calc. for $C_{23}H_{21}N_5O_4$ (431.45): C, 64.03; H, 4.91; N, 16.23; IR (KBr) V_{max}/cm^{-1}: 2993 (Ar, C–H), 1586 (C═C), 1598 (C═N, oxadiazolyl), 1515 (N═O), 1569 (C═N); ^1H NMR ($CDCl_3$) δ: 2.32 (s, 3H, CH3), 2.01 (s, 3H, N═C–CH_3), 3.65 (s, 3H, OCH_3), 6.5–7.23 (m, 8H, aromatic). 7.35–7.98 (m, 4H, pyridinyl); MS (*m*/*z*): 432 (M + 1), 433 (M + 2).

*2.1.22. N-{(1Z)-1-[2-methyl-2-(4-nitrophenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-aniline (**PSMB7**)*
Yield 72%, m.p. 179–180 °C; found: C, 64.94; H, 4.76; N, 17.85. Calc. for $C_{22}H_{19}N_5O_3$ (401.43): C, 65.83; H, 4.77; N, 17.45; IR (KBr) V_{max}/cm^{-1}: 2988 (Ar, C–H), 1579 (C═C), 1596 (C═N, oxadiazolyl), 1518 (N═O), 1577 (C═N); ^1H NMR ($CDCl_3$) δ: 2.29 (s, 3H, CH_3), 2.03 (s, 3H, N═C–CH_3), 7.1–7.23 (m, 9H, aromatic). 7.35–8.12 (m, 4H, pyridinyl); MS (*m*/*z*): 402 (M + 1), 403 (M + 2).

*2.1.23. N-{(1Z)-1-[2-methyl-2-(4-nitrophenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-4-nitroaniline (**PSMB8**)*
Yield 70%, m.p. 194–195 °C; found: C, 60.25; H, 4.12; N, 19.15. Calc. for $C_{22}H_{18}N_6O_5$ (446.43): C, 59.19; H, 4.06; N, 18.83; IR (KBr) V_{max}/cm^{-1}: 2983 (Ar, C–H), 1584 (C═C), 1593 (C═N, oxadiazolyl), 1522 (N═O), 1575 (C═N); ^1H NMR ($CDCl_3$) δ: 2.27 (s, 3H, CH_3), 2.1 (s, 3H, N═C–CH_3), 7.4–7.60 (m, 8H, aromatic). 7.66–8.13 (m, 4H, pyridinyl); MS (*m*/*z*) 447 (M + 1), 448 (M + 2).

*2.1.24. N-{(1Z)-1-[2-methyl-2-(4-nitrophenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-4-methoxyaniline (**PSMB9**)*
Yield 67%, m.p. 178–179 °C; found: C, 63.94; H, 5.04; N, 16.65. Calc. for $C_{23}H_{21}N_5O_4$ (431.45): C, 64.03; H, 4.91; N,

Table 2 Pulmonary vein relaxant activity of PSMB1–PSMB15.

Compounds	Difference in tension (grams)mean ± SEM	% Relaxation (compared with standard)
PSMB1	0.04 ± 0.0070	22.2
PSMB2	0.02 ± 0.0031	11.1
PSMB3	0.026 ± 0.004	14.44
PSMB4	0.028 ± 0.0037	15.55
PSMB5	0.042 ± 0.0066	23.33
PSMB6	0.03 ± 0.0031	16.66
PSMB7	0.082 ± 0.0037	45.55
PSMB8	0.082 ± 0.0037	45.55
PSMB9	0.15 ± 0.0037*	83.33*
PSMB10	0.028 ± 0. 0037	15.55
PSMB11	0.038 ± 0.0037	21.11
PSMB12	0.04 ± 0.0070	22.22
PSMB13	0.07 ± 0.0044	38.88
PSMB14	0.05 ± 0.0031	27.77
PSMB15	0.032 ± 0.0058	17.77

* $p < 0.01$, significant, alcohol – control, isosorbide dinitrate-standard drug.

16.23; IR (KBr) V_{max}/cm^{-1}: 2983 (Ar, C–H), 1584 (C═C), 1593 (C═N, oxadiazolyl), 1524 (N═O), 1575 (C═N); ^1H NMR ($CDCl_3$) δ: 2.31 (s, 3H, CH3), 2.04 (s, 3H, N═C–CH_3), 3.75 (s, 3H, OCH_3), 7.2–7.5 (m, 8H, aromatic). 7.6–7.9 (m, 4H, pyridinyl); MS (*m*/*z*): 432 (M + 1), 433 (M + 2).

*2.1.25. N-{(1Z)-1-[2-methyl-2-(4-nitrophenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-1-napthylamine (**PSMB10**)*

Yield 68%, m.p. 172–173 °C; found: C, 69.45; H, 4.56; N, 15.75. Calc. for $C_{26}H_{21}N_5O_3$ (451.49): C, 69.17; H, 4.69; N, 15.51; IR (KBr) V_{max}/cm^{-1}: 2979 (Ar, C–H), 1579 (C═C), 1590 (C═N, oxadiazolyl), 1519 (N═O), 1573 (C═N); ^1H NMR ($CDCl_3$) δ: 2.30 (s, 3H, CH_3), 2.02 (s, 3H, N═C-CH_3), 7.34–7.68 (m, 11H, aromatic), 7.74–8.23 (m, 4H, pyridinyl); MS (*m*/*z*): 452 (M + 1), 453 (M + 2).

*2.1.26. N-{(1Z)-1-[2-methyl-2-(3-nitrophenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-aniline (**PSMB11**)*

Yield 69%, m.p. 185–186 °C; found: C, 64.65; H, 4.67; N, 17.65. Calc. for $C_{22}H_{19}N_5O_3$ (401.43): C, 65.83; H, 4.77; N, 17.45; IR (KBr) V_{max}/cm^{-1}: 2988 (Ar, C–H), 1578 (C═C), 1596 (C═N, oxadiazolyl), 1528 (N═O), 1578 (C═N); ^1H NMR ($CDCl_3$) δ: 2.31 (s, 3H, CH_3), 2.03 (s, 3H, N═C-CH_3), 7.2–7.38 (m, 9H, aromatic), 7.4–8.2 (m, 4H, pyridinyl); MS (*m*/*z*): 402 (M + 1), 403 (M + 2).

*2.1.27. N-{(1Z)-1-[2-methyl-2-(3-nitrophenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-4-nitroaniline (**PSMB12**)*

Yield 73%, m.p. 199–200 °C; found: C, 58.45; H, 4.16; N, 17.85. Calc. for $C_{22}H_{18}N_6O_5$ (446.43): C, 59.19; H, 4.06; N, 18.83; IR (KBr) V_{max}/cm^{-1}: 3012 (Ar, C–H), 1586 (C═C), 1598 (C═N, oxadiazolyl), 1533 (N═O), 1575 (C═N); ^1H NMR ($CDCl_3$) δ: 2.32 (s, 3H, CH_3), 2.01 (s, 3H, N═C–CH_3), 7.2–7.38 (m, 8H, aromatic), 7.45–8.10 (m, 4H, pyridinyl); MS (*m*/*z*): 447 (M + 1) 448 (M + 2).

*2.1.28. N-{(1Z)-1-[2-methyl-2-(3-nitrophenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-p-toludine (**PSMB13**)*

Yield 70%, m.p. 205–206 °C; found: C, 67.09; H, 5.10; N, 16.65. Calc. for $C_{23}H_{21}N_5O_3$ (415.46): C, 66.49; H, 5.09; N, 16.86; IR (KBr) V_{max}/cm^{-1}: 2987 (Ar, C–H), 1578 (C═C), 1599 (C═N, oxadiazolyl), 1575 (C═N), 1535 (N═O); ^1H NMR ($CDCl_3$) δ: 2.32 (s, 3H, CH_3), 2.35 (s, 3H, Ar–CH_3), 2.05 (s, 3H, N═C–CH_3), 7.12–7.45 (m, 8H, aromatic). 7.48–7.97 (m, 4H, pyridinyl); MS (*m*/*z*): 416 (M + 1), 417 (M + 2).

*2.1.29. N-{(1Z)-1-[2-methyl-2-(3-nitrophenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-4-methoxyaniline (**PSMB14**)*

Yield 63%, m.p. 184–185 °C; found: C, 63.85; H, 5.10; N, 16.35. Calc. for $C_{23}H_{21}N_5O_4$ (431.45): C, 64.03; H, 4.91; N, 16.23; IR (KBr) V_{max}/cm^{-1}: 2986 (Ar, C–H), 1583 (C═C), 1597 (C═N, oxadiazolyl), 1529 (N═O), 1576 (C═N); ^1H NMR ($CDCl_3$) δ:2.34 (s, 3H, CH_3), 2.04 (s, 3H, N═C–CH_3), 3.76 (s, 3H, OCH_3), 7.3–7.67 (m, 8H, aromatic), 7.7–8.2 (m, 4H, pyridinyl); MS (*m*/*z*): 432 (M + 1), 433 (M + 2).

*2.1.30. N-{(1Z)-1-[2-methyl-2-(3-nitrophenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-3(2H)-yl]ethylidene}-1-napthylamine (**PSMB15**)*

Yield 64%, m.p. 169–170 °C; found: C, 70.85; H, 5.10; N, 15.62. Calc. for $C_{26}H_{21}N_5O_3$ (451.49): C, 69.17; H, 4.69; N, 15.51; IR (KBr) V_{max}/cm^{-1}: 2989 (Ar, C–H), 1587 (C═C), 1599 (C═N, oxadiazolyl), 1517 (N═O), 1572 (C═N); ^1H NMR ($CDCl_3$) δ: 2.29 (s, 3H, CH_3), 2.04 (s, 3H, N═C–CH_3), 7.37–7.71 (m, 11H, aromatic), 7.74–8.28 (m, 4H, pyridinyl); MS (*m*/*z*): 452 (M + 1), 453 (M + 2).

2.2. Pulmonary vein relaxant activity

The synthesized compounds **PSMB1**–**PSMB15** were tested in vitro for their pulmonary vein relaxant activity. Pulmonary veins and arteries of adult goat of either sex were brought from a local slaughterhouse. The Media used to carry the muscle was ice-cold Krebs–Henseleit solution. These were cut into spiral strips and were used within 12–24 h. These strips were mounted in 15 ml isolated organ baths, containing Krebs–Henseleit solution, mixed with 95% O_2 and 5% CO_2 at 37 °C. The composition of the Krebs–Henseleit solution was (mmol/l): NaCl (118), KCI (4.70), and $CaCI_2$, $2H_2O$ (2.5), KH_2PO_4 (1.2), $MgSO_4$, $7H_2O$ (1.2), $NaHCO_3$ (25.0) and glucose 10.0. The strip was allowed to equilibrate for 2 h under a resting load of 2 g. Relaxation of muscle strip was recorded for each drug using force transducer multichannel physiograph (**BIOPAC MP35 SYSTEM**). The title compounds were compared with isosorbide dinitrate, a standard drug used for relaxation. Alcohol was used as control. Significance was calculated by using ANOVA followed by the Dunnet '*t*' test. The relaxation activity data for all compounds are given in Table 2.

3. Result and discussion

The various title compounds **PSMB1**–**PSMB15** were synthesized cleanly and in fairly good yields. Their structures were

confirmed by an elemental analysis and spectral data. The IR spectrum of these compounds showed C=N str. at around 1575 and 1595 cm^{-1} and alkyl stretching at 3010 cm^{-1}. The compound also exhibited appropriate peaks at the corresponding δ (ppm) (see spectral data) in their ^1H NMR spectra, thus confirming their structures. All the synthesized compounds were screened for their pulmonary vein relaxation activity using goat pulmonary vein. As seen in Table 2, compound **PSMB9** was found to be the most potent, demonstrating 83.33% relaxation as that of isosorbide dinitrate where as compound **PSMB2** was the least potent, exhibiting 11.1% relaxation. The results of the relaxant activity indicate that the presence of parasubstituted aryl ring, with electron withdrawing groups such as 4-nitrophenyl, at C_2 atom of oxadiazole, along with the moderate electron donating substituent at N_3 position appear to be essential for pulmonary vein relaxation.

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