Med Chem Res
DOI 10.1007/s00044-013-0884-x

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antioxidant activity of amido-linked benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrroles and pyrazoles

Suram Durgamma · Akkarapalli Muralikrishna · Venkatapuram Padmavathi · Adivireddy Padmaja

Received: 19 August 2013 / Accepted: 15 November 2013

Abstract The amido-linked benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrroles and benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrazoles were prepared from the synthetic intermediates (*E*)-*N*-(benzoxazol-2-yl)cinnamamide/(*E*)-*N*-(benzothiazol-2-yl)cinnamamide/(*E*)-*N*-(1*H*-benzimidazol-2-yl)cinnamamides adopting simple and versatile synthetic methodologies. All the new compounds were tested for antioxidant activity. The compounds **5b**, **8b** and **14b** displayed greater antioxidant activity when compared with the standard drug ascorbic acid. It was also observed that benzoxazolyl amido-linked derivatives displayed greater radical scavenging activity than the benzothiazolyl and benzimidazolyl amido-linked derivatives.

Keywords Benzoxazole · Benzothiazole · Benzimidazole · Pyrrole · Pyrazole · Antioxidant activity

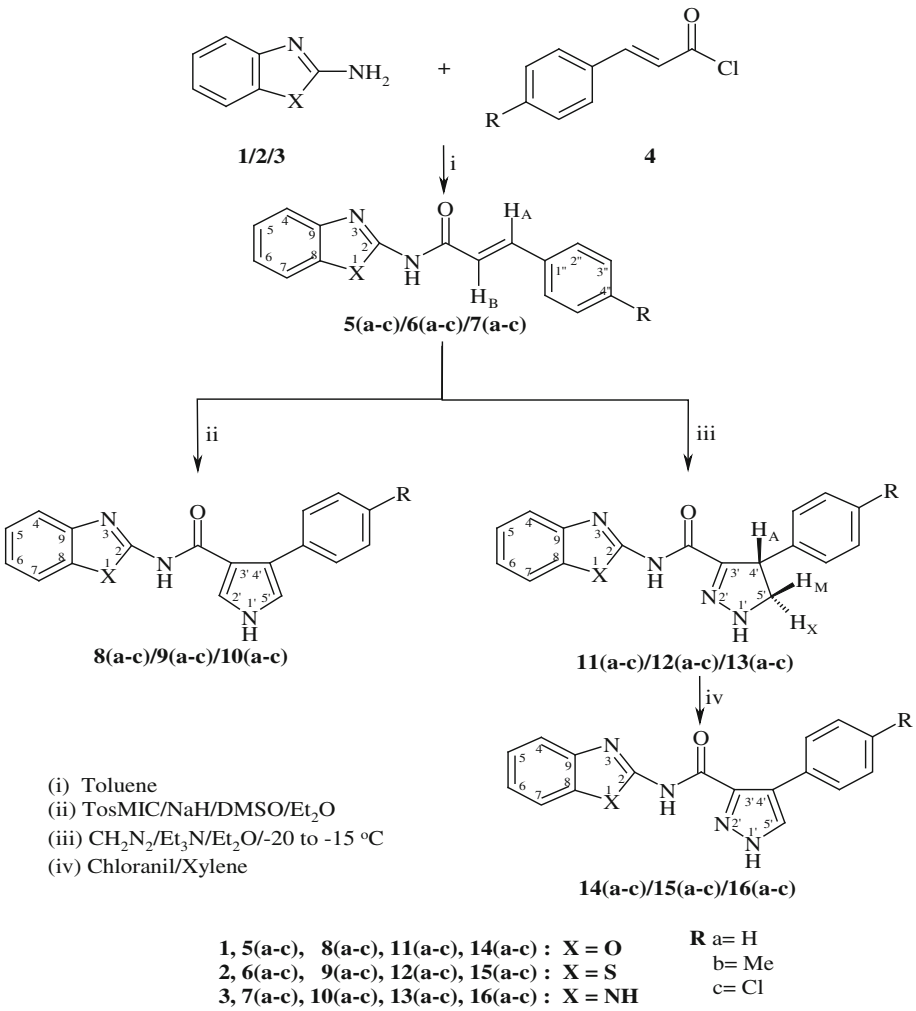
Introduction

Scientific efforts have continuously been directed towards the synthesis of five membered heterocycles because of their vital role as drugs and pharmaceutical agents. Benzoxazole, benzothiazole and benzimidazole motifs are found in several important natural products (Easmon *et al*., 2006; Kumar *et al*., 2002) and have many applications in the field of medicinal chemistry (Ajay and Govindasamy, 2010; Venkatesh and Pandeya, 2009; Padmavathi *et al*., 2012; Akhilesh and Swati, 2010; Hanan, 2010; Heba, 2011). Substituted benzoxazoles possess diverse chemotherapeutic activities viz., antimicrobial (Oren *et al*., 1997; Oren *et al*., 1999; Temiz-Arpaci *et al*., 2002, 2005; Vinsova *et al*., 2005), antiviral (Akbay *et al*., 2003) and antitumour (Ukei and Taniguchi, 1997; Varga *et al*., 2005). Benzothiazoles display a wide range of biological activities viz., antitumour (Chua *et al*., 1999), anti-inflammatory (Paramashivappa *et al*., 2003), analgesic (Westaway *et al*., 2008), antimicrobial (Yildiz-Oren *et al*., 2004), anticonvulsant (Ucar *et al*., 1998) and antimalarial (Takasu *et al*., 2002). The benzimidazole exhibits clinical value towards breast cancer (Andrzejewska *et al*., 2002; Gumus *et al*., 2003; Kamal *et al*., 2004; Chauhan *et al*., 2005), leukaemia (Garuti *et al*., 2000; Demirayak *et al*., 2002), tumour cells (Lukevics *et al*., 2001; Handratta *et al*., 2005), etc. Pyrroles are the fundamental structural motifs in various classes of natural and biologically important molecules like porphyrins, bile pigments, coenzymes and alkaloids (Boger *et al*., 1999; Fan *et al*., 2008). Nitropsin and distamycin are pyrrole polyamides and are naturally occurring anticancer antibiotics (Wemmer, 1999). In the literature, multistep synthetic routes of 3,4-disubstituted pyrroles have been reported either by coupling of imines and nitroalkanes or using Friedel–Craft's acylation with an electron-withdrawing group on the pyrrole nitrogen or 3,4-silylated precursors (Shiraishi *et al*., 1999; Zelikin *et al*., 1999; Liu *et al*., 2000). 3,4-Disubstituted pyrroles have also been synthesized from Michael acceptors with tosyl methyl isocyanide (TosMIC) (Van Leusen *et al*., 1972; Pavri and Trudell, 1997; Padmavathi *et al*., 2004). Several pyrazole derivatives exhibit a wide range of biological activities such as potential HIV-1 inhibitors (Larsen *et al*., 1999), insecticides (Arrieta *et al*., 1998), fungicides (Arrieta *et al*., 1998), antiviral (Rashad *et al*., 2008), antihyperglycemic (Kees *et al*., 1996), anti-inflammatory (Penning *et al*., 1997), antiobesity (Rinaldi-Carmona *et al*., 1994) and anticancer (Bouabdallah *et al*., 2006). The

S. Durgamma · A. Muralikrishna · V. Padmavathi · A. Padmaja (✉)
Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, Andhra Pradesh, India
e-mail: adivireddyp@yahoo.co.in

Published online: 26 November 2013

Scheme 1 Synthesis of benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrroles and pyrazoles



1,3-dipolar cycloaddition methodology is widely used for the synthesis of pyrazoles using diverse synthons viz., nitrile imines and alkynes (Conti *et al*., 2007), hydrazones and nitro olefins (Palazzino *et al*., 1987; Deng and Mani, 2006), diazo compounds and alkynes (Aggarwal *et al*., 2003) and azomethine imines and alkynes (Washizuka *et al*., 1999; Komatsu *et al*., 2006). Recently, we have studied the antioxidant activity of pyrazolyl oxadiazoles (Mallikarjuna Reddy *et al*., 2013). Prompted by these findings and our continued interest in the synthesis of biologically potent heterocycles (Padmaja *et al*., 2009; Padmaja *et al*., 2011; Muralikrishna *et al*., 2012), it is proposed to synthesize the molecules having different pharmacophore units and to study their antioxidant activity.

Results and discussion

Chemistry

The present communication deals with the synthesis of a new class of amido-linked benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrroles and pyrazoles from benzoxazolyl/benzothiazolyl/benzimidazolyl-styryl amides as depicted in Scheme 1. The starting compounds, benzoxazol-2-amine (**1**)/benzothiazol-2-amine (**2**)/1*H*-benzimidazol-2-amine (**3**), were prepared by the cyclocondensation of 2-aminophenol/2-aminothiophenol/1,2-phenylenediamine with cyanogen bromide in methanol (Saritha *et al*., 2011; Robert *et al*., 2010). Besides, the cinnamoyl chloride (**4**) was obtained by the chlorination of cinnamic acid with thionyl chloride (Vogel, 1989).

The synthetic intermediates (*E*)-*N*-(benzoxazol-2-yl)cinnamamide (**5a**–**5c**), (*E*)-*N*-(benzothiazol-2-yl)cinnamamide (**6a**–**6c**) and (*E*)-*N*-(1*H*-benzimidazol-2-yl)cinnamamide (**7a**–**7c**) were prepared by the condensation of compounds **1**, **2** and **3** with cinnamoyl chloride in toluene. The ^{1}H NMR spectra of **5a**, **6a** and **7a** showed two doublets at δ 6.72, 6.78, 6.68 and 7.85, 7.86, 7.74 ppm which were assigned to olefin protons (H_A and H_B). The downfield signal was attributed to H_A. The coupling constant, $J \approx 16.0$ Hz indicated that they are in *trans* geometry. A broad singlet was also observed at δ 8.32, 8.38 and 8.18 ppm due to NH in **5a**, **6a** and **7a**, respectively.

Table 1 The in vitro antioxidant activity of compounds **5(a–c)–16(a–c)** in DPPH method

Compounds	Concentration			IC_{50} (μmol/ml)
	50 μg/ml	75 μg/ml	100 μg/ml	
5a	71.45 ± 0.17	73.48 ± 0.16	76.59 ± 0.11	0.105 ± 0.78
5b	79.12 ± 0.08	81.79 ± 0.06	83.56 ± 0.03	0.111 ± 0.63
5c	60.58 ± 0.37	62.18 ± 0.32	64.72 ± 0.27	0.119 ± 0.58
6a	57.40 ± 0.43	58.81 ± 0.46	60.11 ± 0.38	0.112 ± 0.61
6b	63.83 ± 0.33	67.69 ± 0.25	68.24 ± 0.22	0.118 ± 0.57
6c	50.53 ± 0.57	52.75 ± 0.52	56.80 ± 0.47	0.126 ± 0.42
7a	38.12 ± 0.74	42.31 ± 0.68	44.41 ± 0.67	0.105 ± 0.78
7b	44.37 ± 0.67	46.72 ± 0.63	49.81 ± 0.60	0.110 ± 0.62
7c	35.23 ± 0.97	38.46 ± 0.82	40.69 ± 0.75	0.119 ± 0.58
8a	65.74 ± 0.28	68.52 ± 0.23	70.98 ± 0.15	0.121 ± 0.44
8b	75.18 ± 0.11	79.67 ± 0.08	82.35 ± 0.05	0.127 ± 0.41
8c	58.15 ± 0.41	59.53 ± 0.40	61.87 ± 0.35	0.135 ± 0.34
9a	52.72 ± 0.54	55.24 ± 0.45	58.04 ± 0.41	0.128 ± 0.40
9b	62.20 ± 0.30	64.75 ± 0.27	66.24 ± 0.24	0.133 ± 0.36
9c	45.36 ± 0.65	48.24 ± 0.61	50.52 ± 0.55	0.141 ± 0.28
10a	36.67 ± 0.77	39.70 ± 0.71	41.07 ± 0.69	0.120 ± 0.45
10b	41.78 ± 0.71	44.04 ± 0.66	46.28 ± 0.64	0.126 ± 0.42
10c	32.71 ± 1.06	35.09 ± 0.97	37.34 ± 0.86	0.134 ± 0.35
11a	28.65 ± 1.17	31.75 ± 1.09	32.57 ± 1.06	0.122 ± 0.43
11b	31.36 ± 1.09	34.51 ± 0.99	36.42 ± 0.91	0.128 ± 0.40
11c	–	–	–	–
12a	27.32 ± 1.19	30.89 ± 1.14	31.73 ± 1.09	0.129 ± 0.39
12b	30.14 ± 1.14	32.37 ± 1.06	34.26 ± 1.01	0.134 ± 0.35
12c	–	–	–	–
13a	–	–	–	–
13b	25.87 ± 1.21	28.62 ± 1.17	30.05 ± 1.14	0.128 ± 0.40
13c	–	–	–	–
14a	67.31 ± 0.25	70.64 ± 0.18	73.46 ± 0.16	0.121 ± 0.39
14b	78.26 ± 0.12	82.56 ± 0.05	84.91 ± 0.03	0.127 ± 0.37
14c	59.15 ± 0.42	61.36 ± 0.35	63.54 ± 0.31	0.135 ± 0.34
15a	55.26 ± 0.48	57.06 ± 0.42	59.23 ± 0.39	0.128 ± 0.40
15b	62.62 ± 0.32	65.43 ± 0.27	67.68 ± 0.25	0.134 ± 0.36
15c	48.07 ± 0.63	50.12 ± 0.56	52.37 ± 0.40	0.142 ± 0.26
16a	37.93 ± 0.76	40.05 ± 0.70	43.85 ± 0.66	0.121 ± 0.38
16b	42.02 ± 0.69	45.45 ± 0.64	48.19 ± 0.62	0.127 ± 0.46
16c	33.58 ± 1.02	36.12 ± 0.86	39.85 ± 0.73	0.135 ± 0.34
Ascorbic acid	72.58 ± 0.17	75.32 ± 0.11	78.46 ± 0.09	0.256 ± 0.21
Blank	–	–	–	–

(–) Showed no scavenging activity. Values were the mean of three replicates ± SD

Furthermore, the compound **7a** exhibited another broad singlet at δ 12.85 ppm due to NH of benzimidazole ring. The signals of highly acidic protons disappeared on deuteration.

The olefin moiety present in compounds **5(a–c)**, **6(a–c)** and **7(a–c)** was utilised to develop pyrrole and pyrazole rings. Thus, the treatment of compounds **5(a–c)**, **6(a–c)** and **7(a–c)** with tosylmethyl isocyanide (TosMIC) in the presence of sodium hydride in a mixture of dimethyl sulphoxide and ether produced *N*-(benzoxazol-2-yl)-4′-aryl-1′*H*-pyrrole-3′-carboxamide (**8a–8c**), *N*-(benzothiazol-2-yl)-4′-aryl-1′*H*-pyrrole-3′-carboxamide (**9a–9c**) and *N*-(1*H*-benzimidazol-2-yl)-4′-aryl-1′*H*-pyrrole-3′-carboxamide (**10a–10c**), respectively. The ^{1}H NMR spectra of **8a** displayed two singlets at δ 6.80, 7.07, **9a** at 6.84, 7.13 and **10a** at 6.78, 7.03 ppm due to

Table 2 The in vitro antioxidant activity of compounds **5(a–c)**–**16(a–c)** in NO method

Compounds	Concentration		
	50 μg/ml	75 μg/ml	100 μg/ml
5a	74.52 ± 0.12	76.97 ± 0.11	79.62 ± 0.09
5b	82.47 ± 0.05	85.23 ± 0.03	87.56 ± 0.01
5c	61.30 ± 0.32	63.19 ± 0.28	65.88 ± 0.26
6a	57.54 ± 0.43	59.13 ± 0.39	61.70 ± 0.35
6b	66.46 ± 0.27	70.08 ± 0.15	72.19 ± 0.17
6c	53.85 ± 0.50	55.70 ± 0.46	57.42 ± 0.43
7a	43.69 ± 0.68	46.95 ± 0.66	49.03 ± 0.54
7b	48.12 ± 0.63	51.45 ± 0.57	54.24 ± 0.48
7c	38.04 ± 0.83	42.25 ± 0.77	45.48 ± 0.70
8a	69.72 ± 0.23	72.94 ± 0.16	75.28 ± 0.12
8b	77.09 ± 0.10	79.83 ± 0.08	83.21 ± 0.03
8c	58.62 ± 0.40	60.35 ± 0.38	62.31 ± 0.32
9a	54.10 ± 0.49	56.23 ± 0.44	58.37 ± 0.42
9b	62.73 ± 0.30	66.89 ± 0.24	69.92 ± 0.21
9c	50.44 ± 0.56	52.27 ± 0.51	55.58 ± 0.47
10a	39.53 ± 0.81	43.87 ± 0.72	46.12 ± 0.69
10b	45.57 ± 0.67	48.63 ± 0.63	51.72 ± 0.51
10c	36.75 ± 0.91	39.65 ± 0.73	42.61 ± 0.68
11a	32.39 ± 1.06	34.41 ± 1.01	39.82 ± 0.84
11b	34.82 ± 0.99	36.93 ± 0.95	41.37 ± 0.73
11c	–	–	–
12a	31.43 ± 1.09	33.50 ± 1.03	37.28 ± 0.91
12b	33.67 ± 1.02	35.18 ± 0.98	40.53 ± 0.80
12c	–	–	–
13a	–	–	–
13b	30.61 ± 1.14	32.79 ± 1.08	35.94 ± 0.99
13c	–	–	–
14a	72.64 ± 0.17	74.75 ± 0.19	77.06 ± 0.10
14b	80.34 ± 0.06	83.61 ± 0.04	86.78 ± 0.02
14c	60.42 ± 0.33	61.65 ± 0.31	64.67 ± 0.28
15a	56.89 ± 0.45	57.95 ± 0.42	60.21 ± 0.39
15b	64.17 ± 0.28	67.58 ± 0.26	70.43 ± 0.19
15c	51.56 ± 0.52	54.92 ± 0.49	56.14 ± 0.45
16a	42.20 ± 0.79	45.76 ± 0.70	48.05 ± 0.67
16b	47.33 ± 0.65	49.26 ± 0.61	53.08 ± 0.49
16c	37.98 ± 0.85	40.92 ± 0.79	44.74 ± 0.75
Ascorbic acid	76.69 ± 0.11	78.34 ± 0.09	80.45 ± 0.05
Blank	–	–	–

(–) Showed no scavenging activity. Values were the mean of three replicates ± SD

Table 3 The in vitro antioxidant activity of compounds **5(a–c)**–**16(a–c)** in H_2O_2 method

Compounds	Concentration		
	50 μg/ml	75 μg/ml	100 μg/ml
5a	74.15 ± 0.12	76.68 ± 0.11	78.85 ± 0.10
5b	80.43 ± 0.07	84.87 ± 0.03	86.31 ± 0.02
5c	60.79 ± 0.36	62.95 ± 0.32	65.02 ± 0.30
6a	57.12 ± 0.45	59.01 ± 0.38	61.36 ± 0.35
6b	65.43 ± 0.29	67.02 ± 0.25	69.76 ± 0.23
6c	52.75 ± 0.54	54.10 ± 0.49	55.25 ± 0.48
7a	42.14 ± 0.76	44.95 ± 0.71	46.15 ± 0.69
7b	47.26 ± 0.68	49.57 ± 0.64	50.61 ± 0.55
7c	37.28 ± 0.84	41.53 ± 0.71	43.36 ± 0.67
8a	68.48 ± 0.24	71.93 ± 0.17	73.82 ± 0.13
8b	76.70 ± 0.11	78.76 ± 0.09	80.14 ± 0.07
8c	57.41 ± 0.43	59.93 ± 0.37	61.98 ± 0.34
9a	53.80 ± 0.50	55.92 ± 0.47	58.07 ± 0.42
9b	61.76 ± 0.34	63.06 ± 0.31	67.53 ± 0.23
9c	49.13 ± 0.65	50.97 ± 0.56	52.09 ± 0.51
10a	38.50 ± 0.82	42.64 ± 0.77	44.81 ± 0.72
10b	44.93 ± 0.71	47.46 ± 0.69	48.85 ± 0.68
10c	34.65 ± 0.99	39.37 ± 0.73	40.49 ± 0.74
11a	31.32 ± 1.09	34.19 ± 1.01	37.03 ± 0.88
11b	33.14 ± 1.02	37.63 ± 0.86	39.24 ± 0.73
11c	–	–	–
12a	30.21 ± 1.14	33.46 ± 1.03	36.77 ± 0.91
12b	32.56 ± 1.06	35.02 ± 0.98	38.67 ± 0.82
12c	–	–	–
13a	–	–	–
13b	29.83 ± 1.17	32.28 ± 1.08	34.95 ± 0.99
13c	–	–	–
14a	71.52 ± 0.17	73.79 ± 0.12	75.60 ± 0.11
14b	79.51 ± 0.08	83.45 ± 0.04	85.63 ± 0.03
14c	59.63 ± 0.41	61.64 ± 0.34	63.87 ± 0.31
15a	55.85 ± 0.47	57.61 ± 0.41	59.58 ± 0.37
15b	63.90 ± 0.31	66.14 ± 0.27	68.47 ± 0.22
15c	50.44 ± 0.60	51.27 ± 0.52	53.58 ± 0.50
16a	41.89 ± 0.78	43.14 ± 0.75	45.28 ± 0.70
16b	46.31 ± 0.69	48.22 ± 0.68	49.78 ± 0.57
16c	35.41 ± 0.97	40.24 ± 0.75	42.11 ± 0.68
Ascorbic acid	75.64 ± 011	77.62 ± 0.10	79.86 ± 0.08
Blank	–	–	–

(–) Showed no scavenging activity. Values were the mean of three replicates ± SD

$C_{2'}$-H and $C_{5'}$-H. Furthermore, two broad singlets were observed in these compounds at δ 8.25, 8.29, 8.22 due to CONH and at 8.84, 8.92, 8.61 ppm due to NH of pyrrole ring. Apart from these, compound **10a** exhibited another broad singlet at δ 12.68 ppm due to NH of benzimidazole ring. The signals of NH disappeared when D_2O was added.

On the other hand, the reaction of compounds **5(a–c)**, **6(a–c)** and **7(a–c)** with diazomethane in ether in the presence of triethylamine at −20 to −15 °C for 40–48 h resulted in *N*-(benzoxazol-2-yl)-4′,5′-dihydro-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**11a–11c**), *N*-(benzothiazol-2-yl)-4′,5′-dihydro-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**12a–12c**) and

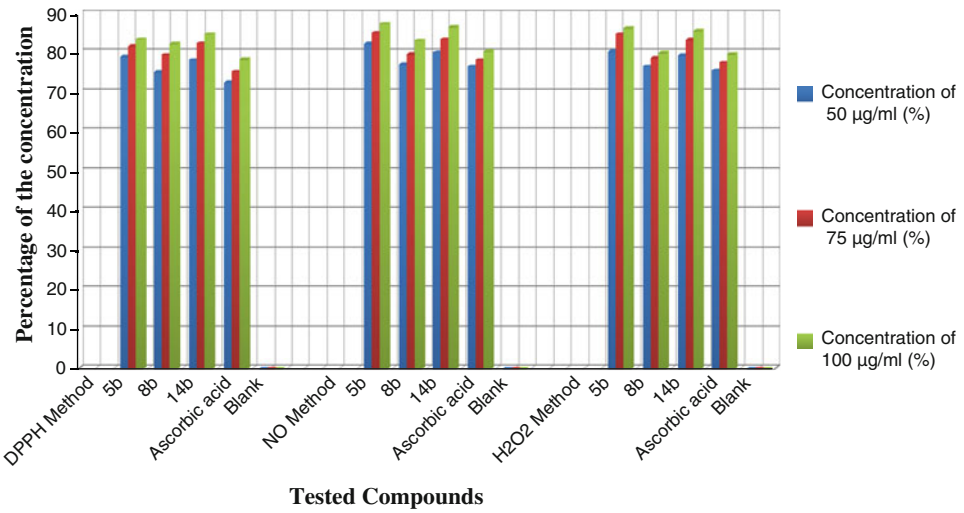


Fig. 1 The in vitro antioxidant activity of **5b**, **8b** and **14b** in all the three methods

N-(1*H*-benzimidazol-2-yl)-4′,5′-dihydro-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**13a–13c**), regioselectively. The ^{1}H NMR spectra of **11a**, **12a** and **13a** exhibited an AMX splitting pattern due to the methine and methylene protons of pyrazoline ring. The three double doublets observed at δ 3.62, 4.00, 4.42 in **11a**, at 3.63, 4.04, 4.64 in **12a** and at 3.59, 3.97, 4.38 ppm in **13a** were assigned to H_X, H_M and H_A, respectively. The coupling constant values $J_{AM} = 12.6$ Hz, $J_{AX} = 6.6$ Hz, $J_{MX} = 10.5$ Hz in **11a**, $J_{AM} = 12.8$ Hz, $J_{AX} = 6.8$ Hz, $J_{MX} = 10.8$ Hz in **12a** and $J_{AM} = 12.4$ Hz, $J_{AX} = 6.3$ Hz, $J_{MX} = 10.2$ Hz in **13a** indicated that H_A, H_M are *cis*, H_A, H_X are *trans* while H_M, H_X are *geminal*. In addition, two broad singlets were appeared at δ 8.40, 9.94 in **11a**, at 8.42, 9.98 in **12a** and at 8.37, 9.83 ppm in **13a** due to CONH and NH of pyrazoline, respectively. Besides, the compound **13a** showed another broad singlet at δ 12.80 ppm due to NH of benzimidazole. The signals due to NH disappeared when D_2O was added.

The oxidation of compounds **11**(**a–c**), **12**(**a–c**) and **13**(**a–c**) with chloranil in xylene produced *N*-(benzoxazol-2-yl)-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**14a–14c**), *N*-(benzothiazol-2-yl)-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**15a–15c**) and *N*-(1*H*-benzimidazol-2-yl)-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**16a–16c**). The absence of an AMX splitting pattern in compounds **14**(**a–c**), **15**(**a–c**) and **16**(**a–c**) indicated that aromatisation took place. The structures of all the new compounds were further characterised by IR, ^{13}C NMR and elemental analyses.

Biological evaluation

Antioxidant activity

The compounds **5**(**a–c**)–**16**(**a–c**) were evaluated for antioxidant property by 2,2,-diphenyl-1-picrylhydrazyl (DPPH) (Burits and Bucar, 2000; Cuendet *et al*., 1997), nitric oxide (NO) (Green *et al*., 1982; Marcocci *et al*., 1994) and hydrogen peroxide (H_2O_2) (Ruch *et al*., 1989) methods. The observed data on the antioxidant activity of the compounds and control drug are presented in Tables 1, 2 and 3. The aim of this study is to identify the potential heterocyclic compound as antioxidant agent. The compounds **5b**, **8b** and **14b** showed excellent radical scavenging activity in all the three methods (Fig. 1) when compared with the standard drug Ascorbic acid. The compounds **5a**, **6b**, **8a**, **9b**, **14a** and **15b** exhibited good activity whereas the compounds **6a**, **6c**, **8c**, **9a**, **14c** and **15a** displayed moderate activity. However, the compounds **11c**, **12c**, **13a** and **13c** showed no activity, while the compounds **5c**, **7a**, **7b**, **7c**, **9c**, **10a**, **10b**, **10c**, **11a**, **11b**, **12a**, **12b**, **13b**, **15c**, **16a**, **16b** and **16c** exhibited least activity. It was also observed that compounds having methyl substituent on the phenyl ring displayed significant activity than unsubstituted and chloro-substituted compounds. Amongst the tested compounds amido-linked styryl (**5a–5c**), pyrrolyl (**8a–8c**) and pyrazolyl (**14a–14c**) compounds exhibited greater activity than the pyrazolinyl (**11a–11c**) derivatives. In fact, the unsaturated compounds (**5a–5c**) showed comparatively higher activity than the pyrrolyl (**8a–8c**) and pyrazolyl (**14a–14c**) derivatives. This may be due to effective conjugation of styryl moiety attached to the amido group. It was also noticed that benzoxazolyl amido-linked derivatives displayed greater activity than the benzothiazolyl and benzimidazolyl amido-linked ones. Besides, the perusal of Tables 1, 2 and 3 indicated that radical scavenging activity increases with increase in concentration in all the three methods.

Conclusion

The amido-linked benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrroles and benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrazoles were prepared from the synthetic

intermediates (*E*)-*N*-(benzoxazol-2-yl)cinnamamide/(*E*)-*N*-(benzothiazol-2-yl)cinnamamide/(*E*)-*N*-(1*H*-benzimidazol-2-yl)cinnamamides adopting simple and versatile synthetic methodologies. All the new compounds were tested for antioxidant activity. The compounds **5b**, **8b** and **14b** displayed greater antioxidant activity when compared with the standard drug ascorbic acid. It was also observed that benzoxazolyl amido-linked derivatives displayed greater activity than the benzothiazolyl and benzimidazolyl amido-linked derivatives.

Experimental

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, hexane/ethyl acetate, 3:1). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wavenumbers were given in cm^{-1}. The ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Jeol JNM λ-400 MHz. The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Jeol JNM spectrometer operating at λ-100 MHz. The mass spectra were recorded on Jeol JMS-D 300 and Finnigan Mat 1210 B at 70 eV with an emission current of 100 μA. All chemical shifts are reported in ppm using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The compounds benzoxazol-2-amine (**1**)/benzothiazol-2-amine (**2**)/1*H*-benzimidazol-2-amine (**3**) and cinnamoyl chloride (**4**) were prepared as per the literature precedent (Saritha *et al*., 2011; Robbert *et al*., 2010; Vogel, 1989).

General procedure for the synthesis of (*E*)-*N*-(benzoxazol-2-yl)cinnamamide (**5a**–**5c**), (*E*)-*N*-(benzothiazol-2-yl)cinnamamide (**6a**–**6c**) and (*E*)-*N*-(1*H*-benzimidazol-2-yl)cinnamamide (**7a**–**7c**)

A mixture of compound **1/2/3** (1 mmol), cinnamoyl chloride (**4**) (1.1 mmol) and toluene (10 ml) were heated to reflux for 15–18 h. After completion of the reaction, the contents were cooled to room temperature. The separated solid was purified by column chromatography (silica gel, ethyl acetate/hexane, 1.5:3).

*(E)-N-(Benzoxazol-2-yl)cinnamamide (**5a**)*

Mp 202–204 °C; yield 65 %; IR (KBr) ν_{max} 3309, 1654, 1618, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.32$ (bs, 1H, NH), 7.85 (d, 1H, H_A, $J = 16.0$ Hz), 7.13–7.35 (m, 9H, Ar–H), 6.72 (d, 1H, H_B, $J = 16.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 168.0$ (CO), 163.1 (C-2), 150.2 (C, C-8), 143.2 (C-H_A), 142.5 (C, C-9), 133.4 (C, C-1″), 128.8 (CH, C-3″), 128.1 (CH, C-4″), 127.3 (CH, C-2″), 124.5 (CH, C-5), 123.5 (CH, C-6), 120.4 (CH, C-4), 117.8 (C-H_B), 117.3 (CH, C-7); MS (*m/z*): 264.28 [$M^{+\cdot}$]. Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.57; N, 10.60. Found: C, 72.64; H, 4.62; N, 10.71.

*(E)-N-(Benzoxazol-2-yl)-3-(4″-methylphenyl)acrylamide (**5b**)*

Mp 195–197 °C; yield 68 %; IR (KBr) ν_{max} 3302, 1651, 1615, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.29$ (bs, 1H, NH), 7.79 (d, 1H, H_A, $J = 15.9$ Hz), 7.11–7.31 (m, 8H, Ar–H), 6.70 (d, 1H, H_B, $J = 15.9$ Hz), 2.34 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 167.1$ (CO), 162.7 (C-2), 149.8 (C, C-8), 142.8 (C-H_A), 142.4 (C, C-9), 137.4 (C, C-4″), 133.5 (C, C-1″), 128.3 (CH, C-3″), 126.8 (CH, C-2″), 125.2 (CH, C-5), 123.4 (CH, C-6), 119.4 (CH, C-4), 117.5 (C-H_B), 117.1 (CH, C-7), 24.6 (Ar-CH_3); MS (*m/z*): 278.31 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.06. Found: C, 73.21; H, 5.13; N, 10.15.

*(E)-N-(Benzoxazol-2-yl)-3-(4″-chlorophenyl)acrylamide (**5c**)*

Mp 212–214 °C; yield 72 %; IR (KBr) ν_{max} 3311, 1658, 1620, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.34$ (bs, 1H, NH), 7.87 (d, 1H, H_A, $J = 16.1$ Hz), 7.15–7.39 (m, 8H, Ar–H), 6.75 (d, 1H, H_B, $J = 16.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.9$ (CO), 163.5 (C-2), 151.3 (C, C-8), 143.5 (C-H_A), 140.3 (C, C-9), 134.8 (C, C-4″), 134.2 (C, C-1″), 128.6 (CH, C-3″), 127.4 (CH, C-2″), 124.7 (CH, C-5), 123.8 (CH, C-6), 120.3 (CH, C-4), 118.2 (C-H_B), 117.8 (CH, C-7); MS (*m/z*): 298.73 [$M^{+\cdot}$]. Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.47; H, 3.77; N, 9.46.

*(E)-N-(Benzothiazol-2-yl)cinnamamide (**6a**)*

Mp 148–150 °C; yield 78 %; IR (KBr) ν_{max} 3318, 1659, 1623, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.38$ (bs, 1H, NH), 7.86 (d, 1H, H_A, $J = 16.2$ Hz), 7.18–8.20 (m, 9H, Ar–H), 6.78 (d, 1H, H_B, $J = 16.2$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.2$ (CO), 166.8 (C-2), 147.3 (C, C-9), 144.8 (C-H_A), 136.5 (C, C-1″), 129.4 (CH, C-3″), 128.7 (CH, C-4″), 127.2 (CH, C-2″), 126.3 (CH, C-6), 126.0 (CH, C-5), 125.3 (C, C-8), 121.9 (CH, C-7), 121.3 (CH, C-4), 118.4 (C-H_B); MS (*m/z*): 280.35 [$M^{+\cdot}$]. Anal.

Calcd. for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.99. Found: C, 68.67; H, 4.25; N, 10.08.

*(E)-N-(Benzothiazol-2-yl)-3-(4″-methylphenyl)acrylamide (**6b**)*

Mp 137–139 °C; yield 75 %; IR (KBr) ν_{max} 3315, 1657, 1619, 1585 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.26$ (bs, 1H, NH), 7.81 (d, 1H, H_A, $J = 16.0$ Hz), 7.16–8.15 (m, 8H, Ar–H), 6.74 (d, 1H, H_B, $J = 16.0$ Hz), 2.36 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 168.8$ (CO), 167.6 (C-2), 146.3 (C, C-9), 144.5 (C-H_A), 136.4 (C, C-4″), 132.4 (C, C-1″), 128.3 (CH, C-3″), 126.2 (CH, C-2″), 125.8 (CH, C-6), 125.4 (CH, C-5), 124.5 (C, C-8), 121.1 (CH, C-7), 120.4 (CH, C-4), 117.9 (C-H_B), 24.8 (Ar-CH_3); MS (*m/z*): 294.38 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.22; H, 4.67; N, 9.47.

*(E)-N-(Benzothiazol-2-yl)-3-(4″-chlorophenyl)acrylamide (**6c**)*

Mp 161–163 °C; yield 71 %; IR (KBr) ν_{max} 3331, 1660, 1625, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.40$ (bs, 1H, NH), 7.89 (d, 1H, H_A, $J = 16.3$ Hz), 7.20–8.23 (m, 8H, Ar–H), 6.85 (d, 1H, H_B, $J = 16.3$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.4$ (CO), 168.6 (C-2), 148.4 (C, C-9), 145.2 (C-H_A), 133.8 (C, C-4″), 133.0 (C, C-1″), 128.4 (CH, C-3″), 127.3 (CH, C-2″), 125.9 (CH, C-6), 125.5 (CH, C-5), 124.6 (C, C-8), 122.1 (CH, C-7), 121.8 (CH, C-4), 118.7 (C-H_B); MS (*m/z*): 314.80 [$M^{+\cdot}$]. Anal. Calcd. for $C_{16}H_{11}ClN_2OS$: C, 61.05; H, 3.52; N, 8.90. Found: C, 60.94; H, 3.59; N, 8.99.

*(E)-N-(1H-Benzimidazol-2-yl)cinnamamide (**7a**)*

Mp 255–257 °C; yield 86 %; IR (KBr) ν_{max} 3302, 1653, 1616, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 12.85$ (bs, 1H, imidazole-NH), 8.18 (bs, 1H, CO–NH), 7.74 (d, 1H, H_A, $J = 15.8$ Hz), 7.10–7.64 (m, 9H, Ar–H), 6.68 (d, 1H, H_B, $J = 15.8$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 167.4$ (CO), 150.4 (C-2), 141.9 (C-H_A), 138.4 (C, C-8, C-9), 134.3 (C, C-1″), 128.9 (CH, C-3″), 128.3 (CH, C-4″), 126.4 (CH, C-2″), 123.5 (CH, C-5, C-6), 119.2 (CH, C-4, C-7), 117.4 (C-H_B); MS (*m/z*): 263.30 [$M^{+\cdot}$]. Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 73.01; H, 4.98; N, 15.96. Found: C, 73.15; H, 5.05; N, 15.84.

*(E)-N-(1H-Benzimidazol-2-yl)-3-(4″-methylphenyl)acrylamide (**7b**)*

Mp 238–240 °C; yield 80 %; IR (KBr) ν_{max} 3297, 1650, 1613, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.82$ (bs, 1H, imidazole-NH), 8.14 (bs, 1H, CO–NH), 7.70 (d, 1H, H_A, $J = 15.7$ Hz), 7.06–7.62 (m, 8H, Ar–H), 6.65 (d, 1H, H_B, $J = 15.7$ Hz), 2.32 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 166.6$ (CO), 150.3 (C-2), 141.6 (C-H_A), 138.1 (C, C-8, C-9), 137.4 (C, C-4″), 128.8 (C, C-1″), 128.1 (CH, C-3″), 126.3 (CH, C-2″), 123.1 (CH, C-5, C-6), 119.0 (CH, C-4, C-7), 117.2 (C-H_B), 24.1 (Ar-CH_3); MS (*m/z*): 277.33 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.50; H, 5.52; N, 15.02.

*(E)-N-(1H-Benzimidazol-2-yl)-3-(4″-chlorophenyl)acrylamide (**7c**)*

Mp 272–275 °C; yield 88 %; IR (KBr) ν_{max} 3305, 1655, 1617, 1598 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.90$ (bs, 1H, imidazole-NH), 8.20 (bs, 1H, CO–NH), 7.79 (d, 1H, H_A, $J = 15.9$ Hz), 7.12–7.69 (m, 8H, Ar–H), 6.70 (d, 1H, H_B, $J = 15.9$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 167.2$ (CO), 150.7 (C-2), 142.0 (C-H_A), 139.1 (C, C-8, C-9), 134.5 (C, C-4″), 129.1 (C, C-1″), 128.7 (CH, C-3″), 126.6 (CH, C-2″), 123.9 (CH, C-5, C-6), 119.4 (CH, C-4, C-7), 117.7 (C-H_B); MS (*m/z*): 297.74 [$M^{+\cdot}$]. Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.55; H, 4.06; N, 14.11. Found: C, 64.44; H, 4.00; N, 14.21.

General procedure for the synthesis of *N*-(benzoxazol-2-yl)-4′-aryl-1′*H*-pyrrole-3′-carboxamide (**8a–8c**), *N*-(benzothiazol-2-yl)-4′-aryl-1′*H*-pyrrole-3′-carboxamide (**9a–9c**) and *N*-(1*H*-benzimidazol-2-yl)-4′-aryl-1′*H*-pyrrole-3′-carboxamide (**10a–10c**)

An equimolar (1 mmol) mixture of compound **5**(**a–c**)/**6**(**a–c**)/**7**(**a–c**) and TosMIC in dimethyl sulphoxide (8 ml) and dry ether (16 ml) was added dropwise via a syringe to a stirred suspension of sodium hydride (50 mg) in dry ether (20 ml). The stirring was continued for 18–21 h at room temperature. After completion of the reaction, the contents were diluted with water and extracted with ether. The ethereal layer was dried (an. Na_2SO_4) and removed in vacuo. The resultant sample was purified by column chromatography (silica gel, ethyl acetate/hexane, 1:3).

*N-(Benzoxazol-2-yl)-4′-phenyl-1′H-pyrrole-3′-carboxamide (**8a**)*

Mp 215–217 °C; yield 69 %; IR (KBr) ν_{max} 3245, 1674, 1620, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.84$ (bs, 1H, NH), 8.25 (bs, 1H, CO–NH), 7.25–7.76 (m, 9H, Ar–H), 7.07 (s, 1H, $C_{5'}$-H), 6.80 (s, 1H, $C_{2'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 166.2$ (CO), 162.5 (C-2), 149.1 (C, C-8), 140.5 (C, C-9), 137.4 (C, C-1″), 132.0 (CH, C-3″), 131.6 (CH, C-4″), 130.4 (CH, C-2″), 129.1 (CH,

C-5), 128.3 (C-4′), 127.2 (CH, C-6), 126.4 (CH, C-4), 121.9 (C-2′), 117.4 (CH, C-7), 116.7 (C-5′), 109.1 (C-3′); MS (*m/z*): 303.32 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85. Found: C, 71.63; H, 4.56; N, 13.62.

*N-(Benzoxazol-2-yl)-4′-(4″-methylphenyl)-1′H-pyrrole-3′-carboxamide (**8b**)*

Mp 204–206 °C; yield 65 %; IR (KBr) ν_{max} 3242, 1665, 1610, 1572 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.78$ (bs, 1H, NH), 8.20 (bs, 1H, CO–NH), 7.18–7.71 (m, 8H, Ar–H), 7.03 (s, 1H, $C_{5'}$-H), 6.78 (s, 1H, $C_{2'}$-H), 2.37 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.0$ (CO), 161.7 (C-2), 149.0 (C, C-8), 140.8 (C, C-9), 137.2 (C, C-4″), 132.7 (C, C-1″), 131.8 (CH, C-3″), 130.1 (CH, C-2″), 129.5 (CH, C-5), 127.6 (C-4′), 127.1 (CH, C-6), 126.2 (CH, C-4), 121.3 (C-2′), 117.3 (CH, C-7), 116.5 (C-5′), 108.7 (C-3′), 23.9 (Ar-CH_3); MS (*m/z*): 317.35 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 72.34; H, 4.91; N, 13.69.

*N-(Benzoxazol-2-yl)-4′-(4″-chlorophenyl)-1′H-pyrrole-3′-carboxamide (**8c**)*

Mp 220–222 °C; yield 71 %; IR (KBr) ν_{max} 3258, 1678, 1622, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.86$ (bs, 1H, NH), 8.27 (bs, 1H, CO–NH), 7.29–7.78 (m, 8H, Ar–H), 7.12 (s, 1H, $C_{5'}$-H), 6.82 (s, 1H, $C_{2'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 166.9$ (CO), 162.8 (C-2), 149.3 (C, C-8), 140.9 (C, C-9), 137.9 (C, C-1″), 132.5 (C, C-4″), 131.7 (CH, C-3″), 130.5 (CH, C-2″), 129.6 (CH, C-5), 128.5 (C-4′), 127.8 (CH, C-6), 126.7 (CH, C-4), 122.1 (C-2′), 117.7 (CH, C-7), 117.0 (C-5′), 109.5 (C-3′); MS (*m/z*): 337.76 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{12}ClN_3O_2$: C, 64.01; H, 3.58; N, 12.44. Found: C, 63.89; H, 3.79; N, 12.82.

*N-(Benzothiazol-2-yl)-4′-phenyl-1′H-pyrrole-3′-carboxamide (**9a**)*

Mp 168–170 °C; yield 62 %; IR (KBr) ν_{max} 3250, 1681, 1624, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.92$ (bs, 1H, NH), 8.29 (bs, 1H, CO–NH), 7.26–8.11 (m, 9H, Ar–H), 7.13 (s, 1H, $C_{5'}$-H), 6.84 (s, 1H, $C_{2'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.5$ (CO), 167.1 (C-2), 148.6 (C, C-9), 136.2 (C, C-1″), 129.8 (CH, C-3″), 129.0 (C-4′), 128.5 (CH, C-4″), 127.4 (CH, C-2″), 125.8 (CH, C-6), 125.2 (CH, C-5), 124.3 (C, C-8), 122.3 (C-2′), 121.4 (CH, C-7), 120.8 (CH, C-4), 117.1 (C-5′), 111.1 (C-3′); MS (*m/z*): 319.39 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{13}N_3OS$: C, 67.69; H, 4.10; N, 13.16. Found: C, 67.98; H, 3.91; N, 13.46.

*N-(Benzothiazol-2-yl)-4′-(4″-methylphenyl)-1′H-pyrrole-3′-carboxamide (**9b**)*

Mp 155–157 °C; yield 60 %; IR (KBr) ν_{max} 3247, 1676, 1616, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.90$ (bs, 1H, NH), 8.22 (bs, 1H, CO–NH), 7.21–8.06 (m, 8H, Ar–H), 7.09 (s, 1H, $C_{5'}$-H), 6.82 (s, 1H, $C_{2'}$-H), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.3$ (CO), 166.8 (C-2), 148.4 (C, C-9), 138.2 (C, C-4″), 133.2 (C, C-1″), 129.4 (CH, C-3″), 128.2 (C-4′), 127.3 (CH, C-2″), 125.7 (CH, C-6), 125.4 (CH, C-5), 123.9 (C, C-8), 122.8 (CH, C-7), 122.2 (C-2′), 121.8 (CH, C-4), 116.8 (C-5′), 110.5 (C-3′), 24.4 (Ar-CH_3); MS (*m/z*): 333.42 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.60; H, 4.76; N, 12.79.

*N-(Benzothiazol-2-yl)-4′-(4″-chlorophenyl)-1′H-pyrrole-3′-carboxamide (**9c**)*

Mp 186–188 °C; yield 64 %; IR (KBr) ν_{max} 3256, 1685, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.95$ (bs, 1H, NH), 8.32 (bs, 1H, CO–NH), 7.29–8.15 (m, 8H, Ar–H), 7.14 (s, 1H, $C_{5'}$-H), 6.88 (s, 1H, $C_{2'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 170.2$ (CO), 167.4 (C-2), 149.4 (C, C-9), 134.8 (C, C-1″), 134.3 (C, C-4″), 129.3 (C-4′), 128.8 (CH, C-3″), 127.9 (CH, C-2″), 125.9 (CH, C-6), 125.5 (CH, C-5), 124.4 (C, C-8), 122.6 (C-2′), 121.7 (CH, C-7), 120.9 (CH, C-4), 117.4 (C-5′), 111.3 (C-3′); MS (*m/z*): 353.83 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{12}ClN_3OS$: C, 61.10; H, 3.42; N, 11.88. Found: C, 61.01; H, 3.59; N, 12.18.

*N-(1H-Benzimidazol-2-yl)-4′-phenyl-1′H-pyrrole-3′-carboxamide (**10a**)*

Mp 284–286 °C; yield 71 %; IR (KBr) ν_{max} 3241, 1666, 1618, 1576 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.68$ (bs, 1H, imidazole-NH), 8.61 (bs, 1H, NH), 8.22 (bs, 1H, CO–NH), 7.22–7.70 (m, 9H, Ar–H), 7.03 (s, 1H, $C_{5'}$-H), 6.78 (s, 1H, $C_{2'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 164.5$ (CO), 152.2 (C-2), 138.5 (C, C-8, C-9), 135.8 (C, C-1″), 129.5 (CH, C-3″), 128.7 (CH, C-4″), 127.8 (C-4′), 127.4 (CH, C-2″), 122.8 (CH, C-5, C-6), 121.5 (C-2′), 118.9 (CH, C-4, C-7), 115.2 (C-5′), 108.8 (C-3′); MS (*m/z*): 302.34 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.87; H, 4.60; N, 18.32.

*N-(1H-Benzimidazol-2-yl)-4′-(4″-methylphenyl)-1′H-pyrrole-3′-carboxamide (**10b**)*

Mp 270–272 °C; yield 64 %; IR (KBr) ν_{max} 3239, 1659, 1615, 1573 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.64$ (bs, 1H, imidazole-NH), 8.58 (bs, 1H, NH), 8.16 (bs, 1H,

CO–NH), 7.19–7.67 (m, 8H, Ar–H), 7.01 (s, 1H, $C_{5'}$-H), 6.73 (s, 1H, $C_{2'}$-H), 2.35 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 163.9$ (CO), 151.5 (C-2), 139.1 (C, C-8, C-9), 138.2 (C, C-4″), 133.4 (C, C-1″), 129.7 (CH, C-3″), 127.8 (CH, C-2″), 127.1 (C-4′), 122.7 (CH, C-5, C-6), 121.2 (C-2′), 118.2 (CH, C-4, C-7), 115.1 (C-5′), 108.6 (C-3′), 23.7 (Ar-CH_3); MS (*m/z*): 316.37 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.23; H, 5.19; N, 18.01.

*N-(1H-Benzimidazol-2-yl)-4′-(4″-chlorophenyl)-1′H-pyrrole-3′-carboxamide (**10c**)*

Mp 292–294 °C; yield 68 %; IR (KBr) ν_{max} 3250, 1672, 1625, 1587 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 12.71$ (bs, 1H, imidazole-NH), 8.63 (bs, 1H, NH), 8.25 (bs, 1H, CO–NH), 7.26–7.73 (m, 8H, Ar–H), 7.06 (s, 1H, $C_{5'}$-H), 6.79 (s, 1H, $C_{2'}$-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.9$ (CO), 152.8 (C-2), 138.6 (C, C-8, C-9), 134.6 (C, C-1″), 134.2 (C, C-4″), 129.4 (CH, C-3″), 128.9 (CH, C-2″), 127.9 (C-4′), 123.1 (CH, C-5, C-6), 121.9 (C-2′), 119.7 (CH, C-4, C-7), 115.5 (C-5′), 109.1 (C-3′); MS (*m/z*): 336.78 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{13}ClN_4O$: C, 64.19; H, 3.89; N, 16.64. Found: C, 64.36; H, 4.01; N, 16.39.

General procedure for the synthesis of *N*-(benzoxazol-2-yl)-4′,5′-dihydro-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**11a**–**11c**), *N*-(benzothiazol-2-yl)-4′,5′-dihydro-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**12a**–**12c**) and *N*-(1*H*-benzimidazol-2-yl)-4′,5′-dihydro-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**13a**–**13c**)

An ice-cold ethereal solution of diazomethane (40 ml, 0.4 M) and triethylamine (0.1 ml) were added to a well-cooled solution of compound **5(a–c)/6(a–c)/7(a–c)** (5 mmol) in dichloromethane (20 ml). The reaction mixture was kept at −20 to −15 °C for 42–48 h. The solvent was removed on a rotary evaporator. The resultant residue was purified by column chromatography (silica gel, ethyl acetate/hexane, 1:4).

*N-(Benzoxazol-2-yl)-4′,5′-dihydro-4′-phenyl-1′H-pyrazole-3′-carboxamide (**11a**)*

Mp 225–227 °C; yield 69 %; IR (KBr) ν_{max} 3278, 1660, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.94$ (bs, 1H, NH), 8.40 (bs, 1H, CO–NH), 7.10–7.42 (m, 9H, Ar–H), 4.42 (dd, 1H, H_A, $J_{AM} = 12.6$ Hz, $J_{AX} = 6.6$ Hz), 4.00 (dd, 1H, H_M, $J_{AM} = 12.6$ Hz, $J_{MX} = 10.5$ Hz), 3.62 (dd, 1H, H_X, $J_{AX} = 6.6$ Hz, $J_{MX} = 10.5$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.8$ (CO), 163.5 (C-2), 149.6 (C, C-8), 149.5 (C-3′), 140.1 (C, C-9), 139.4 (C, C-1″), 128.4 (CH, C-3″), 127.0 (CH, C-2″), 126.5 (CH, C-4″), 124.4 (CH, C-5), 123.8 (CH, C-6), 119.3 (CH, C-4), 117.4 (CH, C-7), 57.9 (C-5′), 48.3 (C-4′); MS (*m/z*): 306.33 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 67.01; H, 4.60; N, 18.69.

*N-(Benzoxazol-2-yl)-4′,5′-dihydro-4′-(4″-methylphenyl)-1′H-pyrazole-3′-carboxamide (**11b**)*

Mp 218–220 °C; yield 66 %; IR (KBr) ν_{max} 3265, 1654, 1565 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.91$ (bs, 1H, NH), 8.38 (bs, 1H, CO–NH), 7.08–7.39 (m, 8H, Ar–H), 4.41 (dd, 1H, H_A, $J_{AM} = 12.4$ Hz, $J_{AX} = 6.4$ Hz), 3.97 (dd, 1H, H_M, $J_{AM} = 12.4$ Hz, $J_{MX} = 10.3$ Hz), 3.61 (dd, 1H, H_X, $J_{AX} = 6.4$ Hz, $J_{MX} = 10.3$ Hz), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.5$ (CO), 163.1 (C-2), 150.1 (C, C-8), 149.1 (C-3′), 140.8 (C, C-9), 137.3 (C, C-1″), 135.2 (C, C-4″), 128.7 (CH, C-3″), 127.3 (CH, C-2″), 124.7 (CH, C-5), 123.6 (CH, C-6), 119.0 (CH, C-4), 117.2 (CH, C-7), 57.6 (C-5′), 47.7 (C-4′), 24.3 (Ar-CH_3); MS (*m/z*): 320.36 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.71; H, 5.20; N, 17.84.

*N-(Benzoxazol-2-yl)-4′,5′-dihydro-4′-(4″-chlorophenyl)-1′H-pyrazole-3′-carboxamide (**11c**)*

Mp 233–235 °C; yield 74 %; IR (KBr) ν_{max} 3300, 1663, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.96$ (bs, 1H, NH), 8.45 (bs, 1H, CO–NH), 7.15–7.47 (m, 8H, Ar–H), 4.45 (dd, 1H, H_A, $J_{AM} = 12.7$ Hz, $J_{AX} = 6.7$ Hz), 4.02 (dd, 1H, H_M, $J_{AM} = 12.7$ Hz, $J_{MX} = 10.6$ Hz), 3.67 (dd, 1H, H_X, $J_{AX} = 6.7$ Hz, $J_{MX} = 10.6$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.9$ (CO), 163.6 (C-2), 149.7 (C-3′), 149.7 (C, C-8), 141.2 (C, C-9), 138.7 (C, C-1″), 131.2 (C, C-4″), 129.0 (CH, C-2″), 128.3 (CH, C-3″), 124.8 (CH, C-5), 123.7 (CH, C-6), 119.5 (CH, C-4), 117.7 (CH, C-7), 58.2 (C-5′), 48.9 (C-4′); MS (*m/z*): 340.77 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.84; N, 16.44. Found: C, 60.22; H, 3.99; N, 16.75.

*N-(Benzothiazol-2-yl)-4′,5′-dihydro-4′-phenyl-1′H-pyrazole-3′-carboxamide (**12a**)*

Mp 180–182 °C; yield 65 %; IR (KBr) ν_{max} 3295, 1665, 1583 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.98$ (bs, 1H, NH), 8.42 (bs, 1H, CO–NH), 7.20–7.58 (m, 9H, Ar–H), 4.64 (dd, 1H, H_A, $J_{AM} = 12.8$ Hz, $J_{AX} = 6.8$ Hz), 4.04 (dd, 1H, H_M, $J_{AM} = 12.8$ Hz, $J_{MX} = 10.8$ Hz), 3.63 (dd, 1H, H_X, $J_{AX} = 6.8$ Hz, $J_{MX} = 10.8$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 168.8$ (CO), 166.7 (C-2), 150.1 (C-3′), 148.1 (C, C-9), 138.8 (C, C-1″), 137.4 (CH, C-3″), 136.9 (CH, C-2″), 135.0 (CH, C-4″), 129.8 (CH, C-6),

129.2 (CH, C-5), 128.2 (C, C-8), 124.6 (CH, C-7), 120.7 (CH, C-4), 58.6 (C-5′), 48.5 (C-4′); MS (*m*/*z*): 322.40 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{14}N_4OS$: C, 63.33; H, 4.38; N, 17.38. Found: C, 63.58; H, 4.49; N, 17.82.

*N-(Benzothiazol-2-yl)-4′,5′-dihydro-4′-(4″-methylphenyl)-1′H-pyrazole-3′-carboxamide (**12b**)*

Mp 168–170 °C; yield 63 %; IR (KBr) ν_{max} 3286, 1661, 1575 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 9.95$ (bs, 1H, NH), 8.40 (bs, 1H, CO–NH), 7.19–7.54 (m, 8H, Ar–H), 4.62 (dd, 1H, H_A, $J_{AM} = 12.5$ Hz, $J_{AX} = 6.4$ Hz), 4.01 (dd, 1H, H_M, $J_{AM} = 12.5$ Hz, $J_{MX} = 10.5$ Hz), 3.60 (dd, 1H, H_X, $J_{AX} = 6.4$ Hz, $J_{MX} = 10.5$ Hz), 2.37 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 168.4$ (CO), 166.2 (C-2), 149.8 (C-3′), 148.7 (C, C-9), 138.4 (C, C-1″), 137.8 (C, C-4″), 137.1 (CH, C-3″), 135.3 (CH, C-2″), 129.7 (CH, C-6), 129.1 (CH, C-5), 128.5 (C, C-8), 124.8 (CH, C-7), 120.1 (CH, C-4), 58.4 (C-5′), 48.4 (C-4′), 24.6 (Ar-CH_3); MS (*m*/*z*): 336.43 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{16}N_4OS$: C, 64.26; H, 4.79; N, 16.65. Found: C, 64.16; H, 4.96; N, 16.87.

*N-(Benzothiazol-2-yl)-4′,5′-dihydro-4′-(4″-chlorophenyl)-1′H-pyrazole-3′-carboxamide (**12c**)*

Mp 197–199 °C; yield 67 %; IR (KBr) ν_{max} 3310, 1670, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 9.99$ (bs, 1H, NH), 8.44 (bs, 1H, CO–NH), 7.27–7.60 (m, 8H, Ar–H), 4.69 (dd, 1H, H_A, $J_{AM} = 12.9$ Hz, $J_{AX} = 6.9$ Hz), 4.06 (dd, 1H, H_M, $J_{AM} = 12.9$ Hz, $J_{MX} = 10.9$ Hz), 3.74 (dd, 1H, H_X, $J_{AX} = 6.9$ Hz, $J_{MX} = 10.9$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.6$ (CO), 166.9 (C-2), 150.5 (C-3′), 148.9 (C, C-9), 138.9 (C, C-1″), 138.1 (C, C-4″), 137.6 (CH, C-2″), 135.7 (CH, C-3″), 130.2 (C, C-8), 129.9 (CH, C-5), 128.6 (CH, C-6), 124.7 (CH, C-7), 120.9 (CH, C-4), 59.5 (C-5′), 49.1 (C-4′); MS (*m*/*z*): 356.84 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{13}ClN_4OS$: C, 57.22; H, 3.67; N, 15.70. Found: C, 57.58; H, 3.65; N, 16.11.

*N-(1H-Benzimidazol-2-yl)-4′,5′-dihydro-4′-phenyl-1′H-pyrazole-3′-carboxamide (**13a**)*

Mp 261–262 °C; yield 70 %; IR (KBr) ν_{max} 3254, 1653, 1568 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.80$ (bs, 1H, imidazole-NH), 9.83 (bs, 1H, NH), 8.37 (bs, 1H, CO–NH), 7.30–7.70 (m, 9H, Ar–H), 4.38 (dd, 1H, H_A, $J_{AM} = 12.4$ Hz, $J_{AX} = 6.3$ Hz), 3.97 (dd, 1H, H_M, $J_{AM} = 12.4$ Hz, $J_{MX} = 10.2$ Hz), 3.59 (dd, 1H, H_X, $J_{AX} = 6.3$ Hz, $J_{MX} = 10.2$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.2$ (CO), 153.6 (C-2), 148.8 (C-3′), 139.7 (C, C-1″), 138.5 (C, C-8, C-9), 129.5 (CH, C-3″), 127.7 (CH, C-2″), 123.4 (CH, C-4″), 122.4 (CH, C-5, C-6), 118.7 (CH, C-4, C-7), 57.7 (C-5′), 47.8 (C-4′); MS (*m*/*z*): 305.34 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{15}N_5O$: C, 66.87; H, 4.95; N, 22.94. Found: C, 67.29; H, 5.07; N, 23.43.

*N-(1H-Benzimidazol-2-yl)-4′,5′-dihydro-4′-(4″-methylphenyl)-1′H-pyrazole-3′-carboxamide (**13b**)*

Mp 249–251 °C; yield 62 %; IR (KBr) ν_{max} 3250, 1650, 1563 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.78$ (bs, 1H, imidazole-NH), 9.80 (bs, 1H, NH), 8.32 (bs, 1H, CO–NH), 7.27–7.64 (m, 8H, Ar–H), 4.35 (dd, 1H, H_A, $J_{AM} = 12.3$ Hz, $J_{AX} = 6.2$ Hz), 3.94 (dd, 1H, H_M, $J_{AM} = 12.3$ Hz, $J_{MX} = 10.1$ Hz), 3.53 (dd, 1H, H_X, $J_{AX} = 6.2$ Hz, $J_{MX} = 10.1$ Hz), 2.31 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 164.9$ (CO), 153.1 (C-2), 148.5 (C-3′), 138.3 (C, C-8, C-9), 137.6 (C, C-1″), 135.2 (C, C-4″), 129.2 (CH, C-3″), 127.5 (CH, C-2″), 123.3 (CH, C-5, C-6), 118.0 (CH, C-4, C-7), 57.5 (C-5′), 47.4 (C-4′), 24.1 (Ar-CH_3); MS (*m*/*z*): 319.36 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{17}N_5O$: C, 67.70; H, 5.36; N, 21.93. Found: C, 67.97; H, 5.54; N, 22.27.

*N-(1H-Benzimidazol-2-yl)-4′,5′-dihydro-4′-(4″-chlorophenyl)-1′H-pyrazole-3′-carboxamide (**13c**)*

Mp 297–299 °C; yield 75 %; IR (KBr) ν_{max} 3295, 1659, 1578 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.85$ (bs, 1H, imidazole-NH), 9.87 (bs, 1H, NH), 8.38 (bs, 1H, CO–NH), 7.32–7.75 (m, 8H, Ar–H), 4.40 (dd, 1H, H_A, $J_{AM} = 12.5$ Hz, $J_{AX} = 6.4$ Hz), 4.02 (dd, 1H, H_M, $J_{AM} = 12.5$ Hz, $J_{MX} = 10.3$ Hz), 3.64 (dd, 1H, H_X, $J_{AX} = 6.4$ Hz, $J_{MX} = 10.3$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.8$ (CO), 153.9 (C-2), 149.4 (C-3′), 138.8 (C, C-8, C-9), 138.4 (C, C-1″), 131.4 (C, C-4″), 129.4 (CH, C-2″), 128.4 (CH, C-3″), 122.8 (CH, C-5, C-6), 119.2 (CH, C-4, C-7), 58.2 (C-5′), 48.3 (C-4′); MS (*m*/*z*): 339.78 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{14}ClN_5O$: C, 60.09; H, 4.15; N, 20.61. Found: C, 60.00; H, 4.24; N, 20.80.

General procedure for the synthesis of *N*-(benzoxazol-2-yl)-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**14a**–**14c**), *N*-(benzothiazol-2-yl)-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**15a**–**15c**) and *N*-(1*H*-benzimidazol-2-yl)-4′-aryl-1′*H*-pyrazole-3′-carboxamide (**16a**–**16c**)

The compound **11**(**a**–**c**)/**12**(**a**–**c**)/**13**(**a**–**c**) (1 mmol), chloranil (1.2 mmol) and xylene (10 ml) were taken and refluxed for 23–25 h. Then it was treated with 5 % NaOH solution. The organic layer was separated and repeatedly washed with water and dried (an. Na_2SO_4). The solvent

was removed in vacuo. The solid obtained was purified by recrystallization from 2-propanol.

*N-(Benzoxazol-2-yl)-4′-phenyl-1′H-pyrazole-3′-carboxamide (**14a**)*

Mp 232–234 °C; yield 72 %; IR (KBr) ν_{max} 3285, 1668, 1620, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.56$ (bs, 1H, CO–NH), 7.24–7.56 (m, 9H, Ar–H), 6.55 (bs, 1H, NH), 6.25 (s, 1H, $C_{5'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.3$ (CO), 163.8 (C-2), 150.1 (C, C-8), 146.8 (C-3′), 142.0 (C, C-9), 136.2 (C, C-1″), 135.7 (C-5′), 129.5 (CH, C-3″), 128.3 (CH, C-4″), 127.0 (CH, C-2″), 124.9 (C-4′), 124.1 (CH, C-5), 123.7 (CH, C-6), 119.7 (CH, C-4), 117.6 (CH, C-7); MS (*m/z*): 304.31 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41. Found: C, 67.47; H, 4.00; N, 18.81.

*N-(Benzoxazol-2-yl)-4′-(4″-methylphenyl)-1′H-pyrazole-3′-carboxamide (**14b**)*

Mp 226–228 °C; yield 61 %; IR (KBr) ν_{max} 3277, 1665, 1615, 1572 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.53$ (bs, 1H, CO–NH), 7.15–7.54 (m, 8H, Ar–H), 6.51 (bs, 1H, NH), 6.17 (s, 1H, $C_{5'}$-H), 2.32 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.1$ (CO), 163.5 (C-2), 149.4 (C, C-8), 146.3 (C-3′), 140.3 (C, C-9), 135.4 (C-5′), 133.8 (C, C-4″), 129.3 (C, C-1″), 127.1 (CH, C-3″), 124.9 (CH, C-2″), 124.1 (C-4′), 123.4 (CH, C-5), 120.1 (CH, C-6), 119.6 (CH, C-4), 117.2 (CH, C-7), 23.7 (Ar-CH_3); MS (*m/z*): 318.34 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 68.20; H, 4.60; N, 17.92.

*N-(Benzoxazol-2-yl)-4′-(4″-chlorophenyl)-1′H-pyrazole-3′-carboxamide (**14c**)*

Mp 253–255 °C; yield 70 %; IR (KBr) ν_{max} 3298, 1670, 1625, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.57$ (bs, 1H, CO–NH), 7.28–7.69 (m, 8H, Ar–H), 6.58 (bs, 1H, NH), 6.29 (s, 1H, $C_{5'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.7$ (CO), 163.9 (C-2), 150.4 (C, C-8), 146.9 (C-3′), 140.6 (C, C-9), 135.9 (C-5′), 134.1 (C, C-1″), 129.0 (C, C-4″), 128.6 (CH, C-3″), 125.2 (C-4′), 124.3 (CH, C-2″), 123.8 (CH, C-5), 120.6 (CH, C-6), 119.9 (CH, C-4), 117.9 (CH, C-7); MS (*m/z*): 338.76 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{11}ClN_4O_2$: C, 60.28; H, 3.27; N, 16.54. Found: C, 60.49; H, 3.33; N, 16.82.

*N-(Benzothiazol-2-yl)-4′-phenyl-1′H-pyrazole-3′-carboxamide (**15a**)*

Mp 187–188 °C; yield 65 %; IR (KBr) ν_{max} 3311, 1680, 1622, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.59$ (bs, 1H, CO–NH), 7.30–7.95 (m, 9H, Ar–H), 6.57 (bs, 1H, NH), 6.32 (s, 1H, $C_{5'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.1$ (CO), 165.6 (C-2), 148.5 (C, C-9), 147.2 (C-3′), 136.6 (C-5′), 135.7 (C, C-1″), 129.4 (CH, C-3″), 128.3 (CH, C-4″), 127.3 (CH, C-2″), 126.2 (C-4′), 125.4 (CH, C-6), 125.2 (CH, C-5), 123.8 (C, C-8), 121.9 (CH, C-7), 121.7 (CH, C-4); MS (*m/z*): 320.38 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{12}N_4OS$: C, 63.73; H, 3.77; N, 17.49. Found: C, 64.18; H, 3.90; N, 17.80.

*N-(Benzothiazol-2-yl)-4′-(4″-methylphenyl)-1′H-pyrazole-3′-carboxamide (**15b**)*

Mp 172–174 °C; yield 62 %; IR (KBr) ν_{max} 3304, 1675, 1617, 1588 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.56$ (bs, 1H, CO–NH), 7.26–7.92 (m, 8H, Ar–H), 6.55 (bs, 1H, NH), 6.30 (s, 1H, $C_{5'}$-H), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.0$ (CO), 165.3 (C-2), 148.3 (C, C-9), 147.0 (C-3′), 137.8 (C, C-4″), 136.1 (C-5′), 135.3 (C, C-1″), 133.2 (CH, C-3″), 129.6 (CH, C-2″), 127.1 (CH, C-6), 126.0 (C-4′), 125.0 (CH, C-5), 124.8 (C, C-8), 121.8 (CH, C-7), 121.3 (CH, C-4), 24.3 (Ar-CH_3); MS (*m/z*): 334.41 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75. Found: C, 64.84; H, 4.38; N, 16.99.

*N-(Benzothiazol-2-yl)-4′-(4″-chlorophenyl)-1′H-pyrazole-3′-carboxamide (**15c**)*

Mp 204–206 °C; yield 68 %; IR (KBr) ν_{max} 3328, 1687, 1628, 1598 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.61$ (bs, 1H, CO–NH), 7.32–8.02 (m, 8H, Ar–H), 6.60 (bs, 1H, NH), 6.38 (s, 1H, $C_{5'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.4$ (CO), 166.2 (C-2), 148.6 (C, C-9), 147.8 (C-3′), 137.9 (C, C-1″), 136.8 (C-5′), 134.1 (C, C-4″), 133.1 (CH, C-3″), 129.0 (CH, C-2″), 128.4 (CH, C-6), 126.7 (C-4′), 125.6 (CH, C-5), 123.7 (C, C-8), 121.5 (CH, C-7), 120.4 (CH, C-4); MS (*m/z*): 354.83 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{11}ClN_4OS$: C, 57.55; H, 3.13; N, 15.71. Found: C, 57.80; H, 3.23; N, 16.09.

*N-(1H-Benzimidazol-2-yl)-4′-phenyl-1′H-pyrazole-3′-carboxamide (**16a**)*

Mp 286–288 °C; yield 72 %; IR (KBr) ν_{max} 3263, 1660, 1610, 1575 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.86$ (bs, 1H, imidazole-NH), 8.54 (bs, 1H, CO–NH), 7.19–7.87 (m, 9H, Ar–H), 6.50 (bs, 1H, NH), 6.18 (s, 1H, $C_{5'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 164.9$ (CO), 154.6 (C-2), 145.3 (C-3′), 139.3 (C, C-8, C-9), 137.8 (C, C-1″), 137.7 (CH, C-3″), 135.5 (C-5′), 130.2 (CH, C-4″), 128.9 (CH, C-2″), 128.6 (CH, C-5, C-6), 124.0 (C-4′), 119.1 (CH, C-4,

C-7); MS (*m/z*): 303.32 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.77; H, 4.47; N, 23.48.

*N-(1H-Benzimidazol-2-yl)-4′-(4″-methylphenyl)-1′H-pyrazole-3′-carboxamide (**16b**)*

Mp 275–276 °C; yield 66 %; IR (KBr) ν_{max} 3252, 1651, 1600, 1569 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.84$ (bs, 1H, imidazole-NH), 8.45 (bs, 1H, CO–NH), 7.15–7.85 (m, 8H, Ar–H), 6.47 (bs, 1H, NH), 6.12 (s, 1H, $C_{5'}$-H), 2.28 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 163.8$ (CO), 153.7 (C-2), 145.1 (C-3′), 139.1 (C, C-8, C-9), 137.6 (C, C-4″), 137.2 (C, C-1″), 135.1 (C-5′), 130.7 (CH, C-3″), 128.5 (CH, C-2″), 128.1 (CH, C-5, C-6), 123.6 (C-4′), 119.4 (CH, C-4, C-7), 23.6 (Ar-CH_3); MS (*m/z*): 317.35 [$M^{+\cdot}$]. Anal. Calcd. for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.75; N, 22.39. Found: C, 68.62; H, 4.76; N, 22.07.

*N-(1H-Benzimidazol-2-yl)-4′-(4″-chlorophenyl)-1′H-pyrazole-3′-carboxamide (**16c**)*

Mp 298–300 °C; yield 75 %; IR (KBr) ν_{max} 3276, 1668, 1614, 1582 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.88$ (bs, 1H, imidazole-NH), 8.56 (bs, 1H, CO–NH), 7.25–7.90 (m, 8H, Ar–H), 6.52 (bs, 1H, NH), 6.20 (s, 1H, $C_{5'}$-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.1$ (CO), 154.8 (C-2), 145.8 (C-3′), 139.9 (C, C-8, C-9), 138.4 (C, C-1″), 137.9 (C, C-4″), 135.8 (C-5′), 130.3 (CH, C-3″), 128.8 (CH, C-2″), 127.7 (CH, C-5, C-6), 124.5 (C-4′), 119.8 (CH, C-4, C-7); MS (*m/z*): 337.76 [$M^{+\cdot}$]. Anal. Calcd. for $C_{17}H_{12}ClN_5O$: C, 60.45; H, 3.58; N, 20.73. Found: C, 60.55; H, 3.69; N, 20.95.

Antioxidant activity

The compounds **5**(**a**–**c**)–**16**(**a**–**c**) were tested for antioxidant property by DPPH (Burits and Bucar, 2000; Cuendet *et al*., 1997), NO (Green *et al*., 1982; Marcocci *et al*., 1994) and H_2O_2 (Ruch *et al*., 1989) methods at three different concentrations 50, 75 and 100 μg/ml.

DPPH radical scavenging activity

The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple-coloured methanol solution of DPPH radical. This property makes it suitable for spectrophotometric studies. To 4 ml of 0.004 % (w/v) methanol solution of DPPH, 1 ml of various concentrations of the test compounds (50, 75 and 100 μg/ml) in methanol were added. After a 30-min incubation period at room temperature, the absorbance was read against blank at 517 nm. Ascorbic acid was used as the standard. The percent of inhibition (*I*%) of free radical production from DPPH was calculated by the following equation

$$I\,\% = [(A_{\text{control}} - A_{\text{sample}})/A_{\text{blank}}] \times 100,$$

where A_{control} is the absorbance of the control reaction (containing methanolic DPPH and ascorbic acid), A_{sample} is the absorbance of the test compound (containing methanolic DPPH and test compound) and A_{blank} is the absorbance of the blank (containing only methanolic DPPH). Tests were carried out in triplicate.

Nitric oxide (NO) scavenging activity

NO scavenging activity was measured by slightly modified methods of Green et al. and Marcocci et al. NO radicals were generated from sodium nitroprusside. 1 ml of sodium nitroprusside (10 mm) and 1.5 ml of phosphate buffer saline (0.2 M, pH 7.4) were added to different concentrations (50, 75 and 100 μg/ml) of the test compounds and incubated for 150 min at 25 °C. After incubation 1 ml of the reaction mixture was treated with 1 ml of Griess reagent (1 % sulphanilamide, 2 % H_3PO_4 and 0.1 % naphthylethylenediamine dihydrochloride). The absorbance of the chromatophore was measured at 546 nm. Ascorbic acid was used as standard. NO scavenging activity was calculated by the following equation:

$$\%\text{ of scavenging} = [(A_{\text{control}} - A_{\text{sample}})/A_{\text{blank}}] \times 100,$$

where A_{control} is the absorbance of the control reaction (containing all reagents and ascorbic acid), A_{sample} is the absorbance of the test compound (containing all reagents and test compound) and A_{blank} is the absorbance of the blank (containing only reagents). Tests were carried out in triplicate.

Hydrogen peroxide (H_2O_2) scavenging activity

The H_2O_2 scavenging ability of the test compound was determined according to the method of Ruch et al. A solution of H_2O_2 (40 mm) was prepared in phosphate buffer (pH 7.4). 50, 75 and 100 μg/ml concentrations of the test compounds in 3.4 ml phosphate buffer were added to H_2O_2 solution (0.6 ml, 40 mm). The absorbance value of the reaction mixture was recorded at 230 nm. The percent of scavenging of H_2O_2 was calculated by the following equation:

$$\%\text{ of scavenging} = [(A_{\text{control}} - A_{\text{sample}})/A_{\text{blank}}] \times 100,$$

where A_{control} is the absorbance of the control reaction (containing all reagents and ascorbic acid), A_{sample} is the absorbance of the test compound (containing all reagents

and test compound) and A_{blank} is the absorbance of the blank (containing only reagents). Tests were carried out in triplicate.

Acknowledgments One of the aurhors (A. Padmaja) is thankful to University Grants Commission (UGC), New Delhi, for financial assistance under a major research project. The authors are also thankful to Prof. Ch. Apparao, Department of Bio-Chemistry, S. V. University, Tirupati, for providing necessary facilities to carry out the antioxidant activity of the compounds.

References

Aggarwal VK, De Vicente J, Bonnert RV (2003) A novel one-pot method for the preparation of pyrazoles by 1,3-dipolar cycloadditions of diazo compounds generated in situ. J Org Chem 68:5381–5383

Ajay BN, Govindasamy S (2010) Synthesis of benzoxazoles by an efficient Ullmann-type intramolecular $C_{(aryl)}$–O bond-forming coupling cyclization with a BINAM-copper(II) catalyst. Synthesis 4:579–586

Akbay A, Oren I, Temiz-Arpaci O, Aki-Sxener E, Yalcin I (2003) Synthesis and HIV-1 reverse transcriptase inhibitor activity of some 2,5,6-substituted benzoxazole, benzimidazole, benzothiazole and oxazolo (4,5-*b*) pyridine derivatives. Arzneim Forsch 54:266–271

Akhilesh G, Swati R (2010) Synthesis and cyclization of benzothiazole: review. J Curr Pharm Res 3:13–23

Andrzejewska M, Yepez-Mulia L, Cedillo-Rivera R, Tapia A, Vilpo L, Vilpo J, Kazimierczuk Z (2002) Synthesis, antiprotozoal and anticancer activity of substituted 2-trifluoromethyl- and 2-pentafluoroethylbenzimidazoles. Eur J Med Chem 37:973–978

Arrieta A, Carrillo JR, Cossio FP, Diaz-Ortiz A, Gomez-Escalonilla MJ, De la Hoz A, Langa F, Moreno A (1998) Efficient tautomerization hydrazone-azomethine imine under microwave irradiation. Synthesis of [4,3′] and [5,3′]bipyrazoles. Tetrahedron 54:13167–13180

Boger DL, Boyce CW, Labroli MA, Sehon CA, Jin Q (1999) Total syntheses of Ningalin A, Lamellarin O, Lukianol A, and Permethyl Storniamide A utilizing heterocyclic azadiene Diel's–Alder reactions. J Am Chem Soc 121:54–62

Bouabdallah I, M'Barek LA, Zyad A, Ramdani A, Zidane L, Melhaoui A (2006) Anticancer effect of three pyrazole derivatives. Nat Prod Res 20:1024–1030

Burits M, Bucar F (2000) Antioxidant activity of *Nigella sativa* essential oil. Phytother Res 14:323–328

Chauhan PMS, Martins CJA, Horwell DC (2005) Syntheses of novel heterocycles as anticancer agents. Bioorg Med Chem 13:3513–3518

Chua M-S, Shi D-F, Wrigley S, Bradshaw TD, Hutchinson I, Shaw PN, Barrett DA, Stanley LA, Stevens MFG (1999) Antitumor benzothiazoles. 7. Synthesis of 2-(4-acylaminophenyl)-benzothiazoles and investigations into the role of acetylation in the antitumor activities of the parent amines. J Med Chem 42:381–392

Conti P, Pinto A, Tamborini L, Rizzo V, Micheli CD (2007) A regioselective route to 5-substituted pyrazole- and pyrazoline-3-phosphonic acids and esters. Tetrahedron 63:5554–5560

Cuendet M, Hostettmann K, Potterat O (1997) Iridoid glucosides with free radical scavenging properties from *Fagraea blumei*. Helv Chim Acta 80:1144–1152

Demirayak S, Mohsen UA, Karaburun AC (2002) Synthesis and anticancer and anti-HIV testing of some pyrazino[1,2-*a*]benzimidazole derivatives. Eur J Med Chem 37:255–260

Deng X, Mani NS (2006) Reaction of *N*-monosubstituted hydrazones with nitroolefins: a novel regioselective pyrazole synthesis. Org Lett 8:3505–3508

Easmon J, Purstinger G, Thies KS, Heinisch G, Hofmann J (2006) Synthesis, structure-activity relationships and antitumor studies of 2-benzoxazolyl hydrazones derived from alpha-(*N*)-acyl heteroaromatics. J Med Chem 49:6343–6350

Fan H, Peng J, Hamann MT, Hu JF (2008) Lamellarins and related pyrrole-derived alkaloids from marine organisms. Chem Rev 108:264–287

Garuti L, Roberti M, Malagoli M, Rossi T, Castelli M (2000) Synthesis and antiproliferative activity of some benzimidazole-4,7-dione derivatives. Bioorg Med Chem Lett 10:2193–2195

Green LC, Wagner DA, Glogowski J, Skipper PL, Wishnok JS, Tannenbaum SR (1982) Analysis of nitrate, nitrite, and [^{15}N] nitrate in biological fluids. Anal Biochem 126:131–138

Gumus F, Algul G, Eren G, Erolu H, Diril N, Gur S, Ozkul A (2003) Synthesis, cytotoxic activity on MCF-7 cell line and mutagenic activity of platinum(II) complexes with 2-substituted benzimidazole ligands. Eur J Med Chem 38:473–480

Hanan MR (2010) Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives. Eur J Med Chem 45:2949–2956

Handratta VD, Vasaitis TS, Njar VCO, Gediya LK, Kataria R, Chopra P, Farquhar R Jr, Guo Z, Qiu Y, Brodie AMH (2005) Novel C-17-heteroaryl steroidal CYP17 inhibitors/antiandrogens: synthesis, pharmacokinetics and antitumor activity in the LACP4 human prostate cancer xenograft model. J Med Chem 48:2972–2984

Heba SAE (2011) Synthesis, characterization of some benzazoles bearing pyridine moiety: search for novel anticancer agents. Eur J Med Chem 46:4025–4034

Kamal A, Ramulu P, Srinivas O, Ramesh G, Kumar PP (2004) Synthesis of C8-linked pyrrolo[2,1-*c*][1,4]benzodiazepine–benzimidazole conjugates with remarkable DNA-binding affinity. Bioorg Med Chem Lett 14:4791–4794

Kees KL, Fitzgerald JJ Jr, Steiner KE, Mattes JF, Mihan B, Tosi T, Mondoro D, McCaleb ML (1996) New potent antihyperglycemic agents in db/db mice: synthesis and structure–activity relationship studies of (4-substituted benzyl)(trifluoromethyl)pyrazoles and -pyrazolones. J Med Chem 39:3920–3928

Komatsu M, Minakata S, Oderaotoshi Y (2006) 1,4-Sila- and stannatropic strategy for generation of 1,3-dipoles and its application to heterocyclic synthesis. ARKIVOC 7:370–389

Kumar D, Jacob MR, Reynolds MB, Kerwin SM (2002) Synthesis and evaluation of anticancer benzoxazoles and benzimidazoles related to UK-1. Bioorg Med Chem 10:3997–4004

Larsen JS, Zahran MA, Pedersen EB, Nielsen C (1999) Synthesis of triazenopyrazole derivatives as potential inhibitors of HIV-1. Monatsh Chem 130:1167–1173

Liu JH, Chan HW, Wong HNC (2000) Highly regioselective synthesis of 3,4-disubstituted 1H-pyrrole. J Org Chem 65:3274–3283

Lukevics E, Arsenyan P, Shestakova I, Domracheva I, Nesterova A, Pudova O (2001) Synthesis and antitumour activity of trimethylsilylpropyl substituted benzimidazoles. Eur J Med Chem 36:507–515

Mallikarjuna Reddy G, Ramachandra Reddy P, Padmavathi V, Padmaja A (2013) Synthesis and antioxidant activity of a new class of mono- and bis-heterocycles. Arch Pharm Chem Life Sci 346:154–162

Marcocci L, Maguire JJ, Droy-Lefaix MT, Packer L (1994) The nitric oxide-scavenging properties of ginkgo biloba extract EGb 761. Biochem Biophys Res Commun 201:748–755

Muralikrishna A, Venkatesh BC, Padmavathi V, Padmaja A, Kondaiah P, Siva Krishna N (2012) Synthesis, antimicrobial and cytotoxic activities of sulfone linked bis heterocycles. Eur J Med Chem 54:605–614

Oren I, Temiz O, Yalcin I, Sener E, Akin A, Uc.arturk N (1997) Synthesis and microbiological activity of 5 (or) 6-methyl-2-substituted benzoxazole and benzimidazole derivatives. Arzneim Forsch 47:1393–1397

Oren I, Temiz O, Yalcin I, Sener E, Altanlar N (1999) Synthesis and antimicrobial activity of some novel 2,5- and/or 6-substituted benzoxazole and benzimidazole derivatives. Eur J Pharm Sci 7:153–160

Padmaja A, Payani T, Dinneswara Reddy G, Padmavathi V (2009) Synthesis, antimicrobial and antioxidant activities of substituted pyrazoles, isoxazoles, pyrimidine and thioxopyrimidine derivatives. Eur J Med Chem 44:4557–4566

Padmaja A, Rajasekhar C, Muralikrishna A, Padmavathi V (2011) Synthesis and antioxidant activity of oxazolyl/thiazolylsulfonylmethyl pyrazoles and isoxazoles. Eur J Med Chem 46:5034–5038

Padmavathi V, Jagan Mohan Reddy B, Rajagopala Sarma M, Thriveni P (2004) A simple strategy for the synthesis of 3,4-disubstituted pyrroles. J Chem Res 2004:79–80

Padmavathi V, Venkatesh BC, Muralikrishna A, Padmaja A (2012) Synthesis and antioxidant activity of a new class of bis and tris heterocycles. Arch Pharm Chem Life Sci 345:745–752

Palazzino G, Cecchi L, Melani F, Colotta V, Filacchioni G, Martini C, Lucacchini A (1987) 1,3-Diarylpyrazolo[4,5-*c*]-and-[5,4-*c*]quinolin-4-ones. 4. Synthesis and specific inhibition of benzodiazepine receptor binding. J Med Chem 30:1737–1742

Paramashivappa R, Kumar P, Rao PVS, Rao AS (2003) Design, synthesis and biological evaluation of benzimidazole/benzothiazole and benzoxazole derivatives as cyclooxygenase inhibitors. Bioorg Med Chem Lett 13:657–660

Pavri NP, Trudell ML (1997) An efficient method for the synthesis of 3-arylpyrroles. J Org Chem 62:2649–2651

Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, Rogers RS, Rogier DJ, Yu SS, Anderson GD, Burton EG, Cogburn JN, Gregory SA, Koboldt CM, Perkins WE, Seibert K, Veenhuizen AW, Zhang YY, Isakson PC (1997) Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4- methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib). J Med Chem 40:1347–1365

Rashad AE, Hegab MI, Abdel-Megeid RE, Micky JA, Abdel-Megeid FME (2008) Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolopyrimidine derivatives. Bioorg Med Chem 16:7102–7106

Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Neliat G, Caput D, Ferrara P, Soubrie P, Breliere JC, Le Fur G (1994) SR1417 16A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 350:240–244

Robert WH III, Samuel R, Catherine SR, Cynthia B, Steven AR, Andrew TS, Christian M (2010) The chemical synthesis and antibiotic activity of a diverse library of 2-aminobenzimidazole small molecules against MRSA and multidrug-resistant *A. baumannii*. Bioorg Med Chem 18:663–674

Ruch RJ, Cheng SJ, Klaunig JE (1989) Prevention of cytotoxicity and inhibition of intercellular communication by antioxidant catechins isolated from Chinese green tea. Carcinogenesis 10:1003–1008

Saritha G, Sarangapani M, Prasad G, Swathi C (2011) Design, synthesis and biological evaluation of benzoxazole derivatives as cyclooxygensase-2 inhibitors. Der Pharmacia Lettre 3:427–432

Shiraishi H, Nishitani T, Nishihara T, Sakaguchi S, Ishii Y (1999) Regioselective synthesis of alkylpyrroles from imines and nitroalkenes by lanthanide compounds. Tetrahedron 55:13957–13964

Takasu K, Inoue H, Kim HS, Suzuki M, Shishido T, Wataya Y, Ihara M (2002) Rhodacyanine dyes as antimalarials. 1. Preliminary evaluation of their activity and toxicity. J Med Chem 45:995–998

Temiz-Arpaci O, Aki-Sxener E, Yalcin I, Altanlar N (2002) Synthesis and antimicrobial activity of some 2-[*p*-substituted phenyl]benzoxazol-5-ylarylcarboxyamides. Arch Pharm Pharm Med Chem 6:283–288

Temiz-Arpaci O, Ozdemir A, Yalcin I, Yildiz I, Aki-Sxener E, Altanlar N (2005) Synthesis and antimicrobial activity of some 5-[2-(morpholin-4-yl)acetamido] and/or 5-[2-(4-substituted piperazin-1-yl)acetamido]-2-(*p*-substitutedphenyl)benzoxazoles. Arch Pharm Chem Life Sci 338:105–111

Ucar H, Van derpoorten K, Cacciaguerra S, Spampinato S, Stables JP, Depovere P, Isa M, Masereel B, Delarge J, Poupaert JH (1998) Synthesis and anticonvulsant activity of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone derivatives. J Med Chem 41:1138–1145

Ukei M, Taniguchi M (1997) UK-1, a novel cytotoxic metabolite from streptomyces SP. 5:7–02.111. Antibacterial action of dimethyl UK-1. J Antibiot (Tokyo) 50:788–790

Van Leusen AM, Siderius H, Hoogenboom BE, Van Leusen D (1972) A new and simple synthesis of the pyrrole ring system from Michael acceptors and tosylmethyl isocyanides. Tetrahedron Lett 13:5337–5340

Varga A, Aki-Sener E, Yalcin I, Temiz-Arpaci O, Tekiner-Gulbasx B, Cherepnev G, Molnar J (2005) Induction of apoptosis and necrosis by resistance modifiers benzazoles and benzoxazines on tumour cell line mouse lymphoma L5718 mdr + cells18. In Vivo 19:1087–1091

Venkatesh P, Pandeya SN (2009) Synthesis, characterisation and anti-inflammatory activity of some 2-amino benzothiazole derivatives. Int J ChemTech Res 1:1354–1358

Vinsova J, Horak V, Buchta V, Kaustova J (2005) Highly lipophilic benzoxazoles with potential antibacterial activity. Molecules 10:783–793

Vogel AI (1989) A text book of practical organic chemistry, 5th edn. Longman Group UK Ltd, London

Washizuka KI, Nagai K, Minakata S, Ryu I, Komatsu M (1999) Novel generation of azomethine imines from α-silylnitrosamines by 1,4-silatropic shift and their cycloaddition. Tetrahedron Lett 40:8849–8853

Wemmer DE (1999) Ligands recognizing the minor groove of DNA: development and applications. Biopolymers 52:197–211

Westaway SM, Thompson M, Rami HK, Stemp G, Trouw LS, Mitchell DJ, Seal JT, Medhurst SJ, Lappin SC, Biggs J, Wright J, Arpino S, Jerman JC, Cryan JE, Holland V, Winborn KY, Coleman T, Stevens AJ, Davis JB, Gunthorpe MJ (2008) Design and synthesis of 6-phenylnicotinamide derivatives as antagonists of TRPV1. Bioorg Med Chem Lett 18:5609–5613

Yildiz-Oren I, Yalcin I, Aki-Sener E, Ucarturk N (2004) Synthesis and structure–activity relationships of new antimicrobial active multisubstituted benzazole derivatives. Eur J Med Chem 39:291–298

Zelikin A, Shastri VR, Langer R (1999) Facile synthesis of 3-alkylpyrroles. J Org Chem 64:3379–3380