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Antimycobacterial activity of novel 1,2,4-oxadiazole-pyranopyridine/chromene hybrids generated by chemoselective 1,3-dipolar cycloadditions of nitrile oxides

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ABSTRACT

The 1,3-dipolar cycloaddition of nitrile oxides generated in situ from benzohydroximinoyl chloride and triethylamine to 2-aminopyranopyridine-3-carbonitriles and 2-aminochromene-3-carbonitriles occurred chemoselectively furnishing novel 1,2,4-oxadiazole-pyranopyridine/chromene hybrid heterocycles in moderate yields. In vitro screening of these compounds against *Mycobacterium tuberculosis* H37Rv (MTB) disclosed that the 1,2,4-oxadiazole-pyranopyridine hybrids display enhanced activity relative to the 1,2,4-oxadiazole-chromene hybrids. Among the compounds screened, 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(2,4-dichlorophenyl)-8-[(*E*)-(2,4-dichlorophenyl)-methylidene]-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-amine (MIC: 0.31 μM) is 1.2, 15.2 and 24.6 times more active than standard antitubercular drugs, viz. isoniazid, ciprofloxacin and ethambutol, respectively.

1. Introduction

Tuberculosis (TB) is a chronic bacterial infection and most people infected with *Mycobacterium tuberculosis* (MTB) harbor the bacterium without displaying symptoms (latent TB), but some develop into active TB disease. The World Health Organization (WHO) estimates that more than 2 billion people are infected with MTB and 1 in 10 people infected with TB will become sick with active TB in their lifetime. In 2008, 9.4 million new TB cases were reported, out of which 1.8 million people died.[1] Directly observed treatment short-course (DOTS) is presently the mainstay of TB control globally,[2a,b] which employs agents like isoniazid, rifampicin, and the aminoglycoside antibiotic streptomycin.[2c] Correctly applied treatment with DOTS has a success rate of 95% and also prevents the emergence of further multi-drug resistant tuberculosis (MDR-TB). With the increasing TB incidence[3] and the emergence of MDR-TB[4] the development of new TB therapeutics can be considered of great importance.

We have recently embarked on a program on the synthesis of structurally diverse novel heterocycles employing domino, cycloaddition and other reactions, followed by their biological screening, which brought to light various antitubercular leads.[5,6] In particular, one of our studies[7] disclosed that tetrahydro-4*H*-pyrano[3,2-*c*]pyridine derivatives **3** inhibited MTB and MDR-TB in vitro (Scheme 1). This provided the impetus to synthesize compounds **4**, designed by bioisosteric replacement of the *N*-Me group of **3** by a CH_2 and further transformation via 1,3-dipolar cycloaddition with nitrile oxides, which have led to novel heterocyclic hybrids combining the structure of **3** and **4** with 1,2,4-oxadiazole pharmacophores. 1,2,4-Oxadiazoles constitute a versatile class of organic compounds with biological activities such as analgesic,[8] antirhinoviral,[9] antipicornaviral (Pleconaril drug),[10] antioxidant[11] and antiinflammatory.[11] These compounds are also used as angiotensin II receptor antagonists,[12] besides finding utility in plant protection, as liquid crystalline mesophases,[13] and as dipeptide mimics.[14] These observations lead to the conclusion that 1,2,4-oxadiazoles satisfy the definition of privileged scaffolds, that is, molecular frameworks that are able to bind to a diverse array of receptors.[15]

Interestingly, the 1,3-dipolar cycloaddition of nitrile oxides generated in situ from the dehydrohalogenation of *N*-hydroxyarylcarboximidoyl chloride and triethylamine to compounds **3** and **4** proceeded in a chemoselective manner affording the novel 1,2,4-oxadiazole-pyranopyridine/chromene hybrids **5** and **6**, respectively, in moderate yields (Scheme 1). These compounds displayed significantly enhanced in vitro activities against MTB compared to

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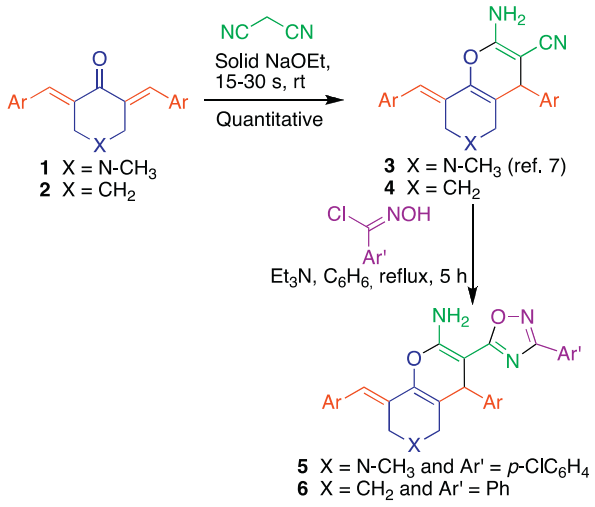

Scheme 1. Synthesis of hybrid compounds **5** and **6**.

their precursors **3** and **4** and these results are presented in this manuscript.

2. Chemistry

In the present paper, the synthesis of compounds **4** in almost quantitative yields (97–99%, Table 1) was achieved in an eco-compatible manner by the reaction of 2,6-*bis*-arylidenecyclohexanones **2** with malononitrile in the presence of solid sodium ethoxide employing solvent-free conditions as described earlier for series **3**,[7] by simply grinding the reaction mixture at ambient temperature (Scheme 1). Previously Jin et al.[16] have reported the synthesis of 2-aminochromene-3-carbonitriles **4a**, **4b**, **4c** and **4f** in 80–93% yields from the reaction of **2** and malononitrile in water for 8 h at 110 °C in the presence of hexadecyltrimethyl ammonium bromide as a phase-transfer catalyst. The latter reaction was reported by Wang et al.[17a] in the presence of KF/Al_2O_3 and by Zhou[17b] under microwave irradiation in the presence of piperidine in ethanol in 71–92% yield. The present expedient synthetic protocol is clearly far more advantageous than the foregoing literature methods with reference to yield, eco-friendliness and cost.

The compounds of series **3** and **4** were subjected to 1,3-dipolar cycloaddition reactions with nitrile oxides generated in situ from *N*-hydroxyarylcarboximidoyl chloride in presence of triethylamine in benzene (Scheme 1).

After completion of the reaction (TLC), the solvent was evaporated in vacuo and the residue, upon column chromatographic purification, afforded 1,2,4-oxadiazole-pyranopyridine/chromene hybrids **5** and **6**, respectively, in 40–65% yields (Table 2). It is pertinent to note that the product of nitrile oxide cycloaddition to the exocyclic alkene moiety of either **3** or **4** was not obtained, even when an excess of nitrile oxide and prolonged reaction times were employed, leading to the conclusion that this cycloaddition occurs chemoselectively on the nitrile function.

The structure of all the products was elucidated with the help of one- and two-dimensional (H,H-COSY, C,H-COSY and HMBC) NMR spectroscopic data and single crystal X-ray crystallographic studies. The ^1H and ^{13}C NMR chemical shifts of 1,2,4-oxadiazole-pyranopyridine/chromene hybrid heterocycles **5** and **6** and the corresponding 2-aminopyranopyridine- and 2-aminochromene-3-carbonitriles **3** and **4** were found to be almost similar, apart from the presence of new signals arising from the 1,2,4-oxadiazole ring and the lack of signal of the nitrile function. The ^1H NMR spectrum of **5g** has singlets for the N-CH_3, NH_2 and benzylidene hydrogen (H-9), respectively, at 2.31, 6.56 and 6.94 ppm and a multiplet for the aromatic hydrogens in the range of 6.87–7.97 ppm. The C,H-COSY correlation of H-9 assigns C-9 to 121.6 ppm. The HMBCs of H-9 (Fig. 1) with the carbon at 55.3 ppm and C-8a at 139.6 ppm assign the former signal at 55.3 ppm to C-7. The C,H-COSY spectrum assigns the 7-CH_2 hydrogens to the doublets at 3.39 and 3.57 ppm (J = 14.8 Hz). The 5-CH_2 hydrogens appear as doublets at 2.85 and 3.12 ppm (J = 15.9 Hz) and show: (i) C,H-COSY correlation with the carbon at 54.5 ppm due to C-5 and (ii) HMBC with C-8a at 139.6 ppm and the carbon at 40.6 ppm due to C-4. From C,H-COSY spectrum, the singlet at 4.42 ppm is readily assigned to H-4. From the HMBCs, the carbon signals at 73.6, 113.9, 156.7 and 175.8 ppm were assigned to C-3, C-4a, C-2 and the C-5 of the 1,2,4-oxadiazole ring, respectively. The carbon signal at 166.0 can be readily assigned to C-3 of 1,2,4-oxadiazole ring.

The proton and carbon signals of **6** have also been assigned similarly. As a representative example, the ^1H and ^{13}C NMR chemical shifts of **6b** are shown in Figure 2. The H-4, NH_2 and benzylidene hydrogens appear as singlets at 4.31, 6.84 and 6.91 ppm, respec-

Table 1
Yields of 2-aminochromene-3-carbonitriles **4**

Compd	Ar	Yield[a] (%)
4a	C_6H_5	99 (93)[b] (92)[c]
4b	*p*-ClC_6H_4	98 (87)[b] (91)[c]
4c	*p*-MeC_6H_4	98 (82)[b]
4d	*p*-$MeOC_6H_4$	99
4e	*p*-FC_6H_4	99
4f	*o*-ClC_6H_4	99 (80)[b]
4g	*o*-MeC_6H_4	98
4h	*o*-$MeOC_6H_4$	98
4i	*m*-$O_2NC_6H_4$	98 (71)[c]
4j	*m*-FC_6H_4	97
4k	2-Thienyl	98
4l	2-Furyl	98
4m	*o*,*p*-$Cl_2C_6H_3$	99
4n	*p*-$Me_2NC_6H_4$	98
4o	Ph-CH=CH	99
4p	1-Naphthyl	99

[a] Yields are quantitative, except the loss during workup.
[b] From Ref. 18.
[c] From Ref. 19.

Table 2
Yield and antimycobacterial activity of **5** and **6** and their respective precursors **3**[a] and **4** against MTB[b]

Compd	Ar	Yield (%)	MIC (μM)		
			5/6		**3/4**
5a	C_6H_5	56	12.28	**3a**	35.21
5b	*p*-ClC_6H_4	61	0.35	**3b**	0.92
5c	*p*-MeC_6H_4	59	3.28	**3c**	16.32
5d	*p*-$MeOC_6H_4$	50	21.97	**3d**	30.12
5e	*o*-MeC_6H_4	47	11.64	**3e**	16.32
5f	*o*-$MeOC_6H_4$	45	5.50	**3f**	15.06
5g	*m*-FC_6H_4	65	0.73	**3g**	0.99
5h	*o*,*p*-$Cl_2C_6H_4$	40	0.31	**3h**	25.36
5i	*p*-$Me_2NC_6H_4$	50	5.26	**3i**	0.43
6a	*p*-ClC_6H_4	40	23.67	**4a**	>25
6b	*p*-$MeOC_6H_4$	52	24.08	**4b**	>25
6c	*p*-FC_6H_4	51	12.63	**4c**	>25
6d	*o*-MeC_6H_4	47	>25.00	**4d**	>25
6e	*o*-$MeOC_6H_4$	41	24.08	**4e**	>25
6f	*m*-FC_6H_4	55	12.63	**4f**	>25
	Rifampicin		0.12	–	–
	Isoniazid		0.36	–	–
	Ciprofloxacin		4.71	–	–
	Ethambutol		7.64	–	–

[a] MIC values taken from our previous work.[7]
[b] MTB: *Mycobacterium tuberculosis*.

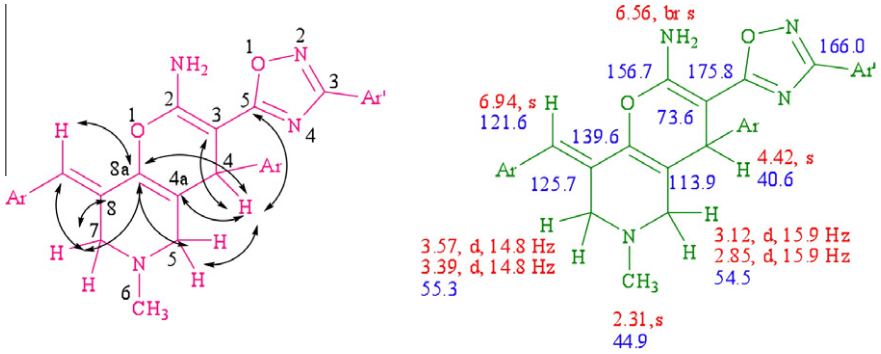

Figure 1. HMBCs, ^{1}H and ^{13}C NMR chemical shifts of **5g**.

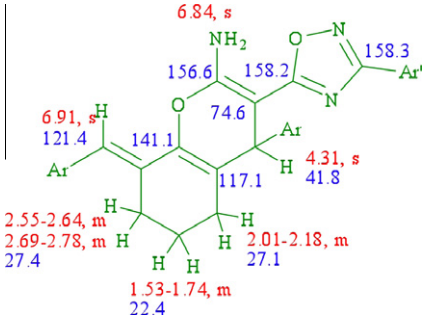

Figure 2. ^{1}H and ^{13}C NMR chemical shifts of **6b**.

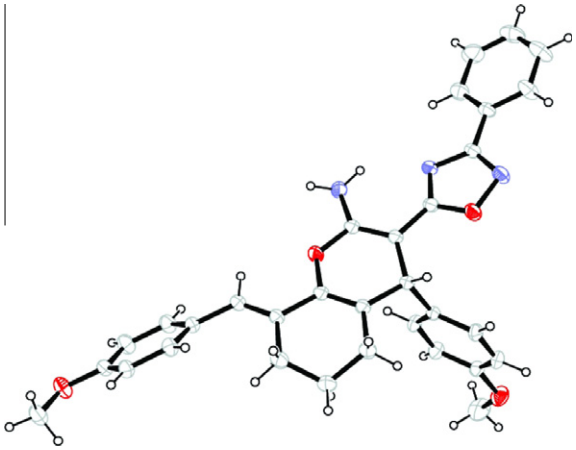

Figure 3. ORTEP diagram of **6b**.

tively. The 6-, 5- and 7-CH_2 hydrogens appeared as multiplets at 1.53–1.74, 2.01–2.18 and 2.55–2.78 ppm, respectively, and their C,H-COSY correlations assign the carbon signals at 22.4, 27.1 and 27.4 ppm to C-6, C-5 and C-7, respectively. The signals at 158.2 and 158.3 arise from the imine carbons of the 1,2,4-oxadiazole ring. The structure of **6b** elucidated from NMR spectroscopic data was further confirmed by a single crystal X-ray crystallographic study (Fig. 3).[18]

3. Pharmacology and structure–activity relationships

The compounds were screened for their in vitro antimycobacterial activity against MTB H37Rv by the agar dilution method[19] for the determination of MIC in triplicates. The MIC is defined as the minimum concentration of compound required to inhibit 99% of bacterial growth, and the MIC values of the synthesized compounds along with the standard drugs for comparison are presented in Table 2. All compounds belonging to series **4** failed to show significant antimycobacterial activity (MIC >25.00 μM), in sharp contrast to series **3**, wherein several compounds displayed good activity,[7] suggesting that N-CH_3 in **3** is a key structural element for antimycobacterial activity. It was also gratifying to note that many compounds of the hybrid heterocycles **5** and **6**, derived from **3** and **4**, respectively, showed enhanced activity against MTB with MICs ranging from 0.31 to >25.00 μM. Six compounds, **5b**, **5c** and **5f–5i** were more potent than the standard drug ethambutol (MIC: 7.64 μM), while four of them **5b**, **5c**, **5g**, and **5h** were more active than ciprofloxacin (MIC: 4.71 μM). Compound **5h**, with a MIC value of 0.31 μM, was found to be the most potent in the library, being 1.2, 15.2, and 24.6 times more active than isoniazid, ciprofloxacin, and ethambutol, respectively. However, all the compounds were less active than rifampicin (MIC: 0.12 μM).

From the structure-MTB activity viewpoint, these results demonstrate that, in general, compounds **5** with three heterocyclic rings are more active than those belonging to series **6** with one carbocyclic ring and two heterocyclic rings (Table 2). A comparison of the activities of series **5** with their precursors **3** show that the antimycobacterial activity is enhanced when the nitrile group in **3** is transformed into the 1,2,4-oxadiazole ring. The data in Table 2 further show that among the compounds screened, **5b**, **5g**, and **5h**, respectively, with *p*-Cl, *m*-F, and *o*,*p*-Cl_2 phenyl rings and **3b**, **3g** and **3i**, respectively, with *p*-Cl, *m*-F, and *p*-Me_2N phenyl rings display maximum potency, showing that the structural dependence of activity of **3** and **5** display slightly different trends.

4. Conclusions

A facile chemoselective synthesis of novel 1,2,4-oxadiazole-pyranopyridine/chromene hybrid heterocycles in moderate yields was realized via the 1,3-dipolar cycloaddition of nitrile oxide to the nitrile function of 2-aminopyranopyridine- and 2-aminochromene-3-carbonitriles, respectively. These compounds display good in vitro antimycobacterial activity against MTB, among which one compound was more potent than the standard first line drugs isoniazid, ciprofloxacin, and ethambutol. The antimycobacterial potency of these compounds renders them attractive leads for further exploration.

5. Experimental

Melting points were measured in open capillary tubes and are uncorrected. The ^{1}H, ^{13}C and 2D-NMR spectra were recorded on a

Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

5.1. General procedure for the synthesis of 4*H*-pyrans 4

A mixture of 2,6-*bis*-arylidenecyclohexanones (**2**, 1 mmol), malononitrile (1 mmol), and sodium ethoxide (1 mmol) was ground well in a mortar at ambient temperature for about 15–30 s. Then water (50–70 mL) was added to the mixture and the product was filtered, washed with water, and dried in vacuo.

5.1.1. 2-Amino-4-(4-methoxyphenyl)-8-[(*E*)-(4-methoxy-phenyl) methylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4d)

White solid, yield 99%, mp 190–191 °C; [found C, 75.05; H, 6.12; N, 6.92. $C_{25}H_{24}N_2O_3$ requires C, 74.98; H, 6.04; N, 7.00%]; δ_H (300 MHz; $CDCl_3$) 1.57–1.69 (2H, m, 6-CH_2), 1.79–2.03 (2H, m, 5-CH_2), 2.52–2.61 (1H, m, 7-CH_2), 2.68–2.76 (1H, m, 7-CH_2), 3.80 (Ar-OCH_3), 3.83 (Ar-OCH_3), 3.91 (1H, s, 4-C*H*), 4.54 (2H, s, NH_2), 6.82 (1H, s, C=C*H*), 6.85–7.27 (8 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 22.2, 27.1, 27.4, 42.7, 55.2, 60.7, 113.6, 114.1, 114.7, 120.1, 122.0, 127.9, 128.9, 129.6, 130.5, 135.1, 141.4, 158.3, 158.7, 158.8.

5.1.2. 2-Amino-4-(4-fluorophenyl)-8-[(*E*)-(4-fluorophenyl)-methylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4e)

White solid, yield 99%, mp 187–188 °C; [found C, 73.32; H, 4.86; N, 7.50. $C_{23}H_{18}F_2N_2O$ requires C, 73.39; H, 4.82; N, 7.44%]; δ_H (300 MHz; $CDCl_3$) 1.60–1.66 (2H, m, 6-CH_2), 1.89–2.05 (2H, m, 5-CH_2), 2.51–2.58 (1H, m, 7-CH_2), 2.66–2.73 (1H, m, 7-CH_2), 3.98 (1H, s, 4-C*H*), 4.59 (2H, s, NH_2), 6.85 (1H, s, C=C*H*), 7.02–7.30 (8 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 22.2, 27.0, 27.4, 42.9, 60.4, 114.3, 119.8, 121.7, 132.3, 141.4, 158.9.

5.1.3. 2-Amino-4-(2-methylphenyl)-8-[(*E*)-(2-methylphenyl)-methylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4g)

White solid, yield 98%, mp 155–156 °C; [found C, 81.44; H, 6.50; N, 7.56. $C_{25}H_{24}N_2O$ requires C, 81.49; H, 6.57; N, 7.60%]; δ_H (300 MHz; $CDCl_3$) 1.66–1.77 (2H, m, 6-CH_2), 1.97–2.14 (2H, m, 5-CH_2), 2.47 (3H, s, Ar-CH_3), 2.50–2.54 (1H, m, 7-CH_2), 2.59 (3H, s, Ar-CH_3), 2.63–2.70 (1H, m, 7-CH_2), 4.49 (1H, s, 4-C*H*), 4.73 (2H, s, NH_2), 7.03 (1H, s, C=C*H*), 7.28–7.40 (8 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 19.4, 20.0, 22.2, 27.0, 27.3, 39.2, 59.6, 115.0, 120.2, 121.4, 125.2, 126.6, 126.9, 128.7, 129.0, 129.4, 129.8, 130.1, 130.5, 135.7, 136.1, 136.6, 140.9, 141.5, 159.0.

5.1.4. 2-Amino-4-(2-methoxyphenyl)-8-[(*E*)-(2-methoxy-phenyl)methylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4h)

White solid, yield 98%, mp 93–95 °C; [found C, 74.91; H, 6.00; N, 7.06. $C_{25}H_{24}N_2O_3$ requires C, 74.98; H, 6.04; N, 7.00%]; δ_H (300 MHz; $CDCl_3$) 1.70–1.78 (2H, m, 6-CH_2), 2.04–2.22 (2H, m, 5-CH_2), 2.64–2.68 (1H, m, 7-CH_2), 2.69–2.76 (1H, m, 7-CH_2), 3.98 (3H, s, Ar-OCH_3), 3.99 (3H, s, Ar-OCH_3), 4.64 (2H, s, NH_2), 4.74 (1H, s, 4-C*H*), 7.08 (1H, s, C=C*H*), 7.00–7.40 (8 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 22.3, 27.2, 29.1, 34.7, 55.9, 56.2, 59.8, 110.5, 110.9, 115.4, 117.0, 117.3, 118.4, 120.3, 128.1, 125.8, 127.3, 128.1, 129.2, 129.6, 131.3, 141.9, 157.0, 157.1, 159.6.

5.1.5. 2-Amino-4-(3-fluorophenyl)-8-[(*E*)-(3-fluorophenyl)-methylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4j)

White solid, yield 97%, mp 168–170 °C; [found C, 73.46; H, 4.74; N, 7.37. $C_{23}H_{18}F_2N_2O$ requires C, 73.39; H, 4.82; N, 7.44%]; δ_H (300 MHz; $CDCl_3$) 1.60–1.68 (2H, m, 6-CH_2), 1.88–2.06 (2H, m, 5-CH_2), 2.51–2.60 (1H, m, 7-CH_2), 2.66–2.74 (1H, m, 7-CH_2), 3.96 (1H, s, 4-C*H*), 4.66 (2H, s, NH_2), 6.84 (1H, s, C=C*H*), 6.93–7.35 (8 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 22.0, 26.7, 27.3, 42.7, 59.6, 114.7, 119.7, 121.2, 130.2, 139.0, 159.0.

5.1.6. 2-Amino-4-(2-thienyl)-8-[(*E*)-2-thienylmethylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4k)

White solid, yield 98%, mp 182–183 °C; [found C, 64.69; H, 4.51; N, 7.88. $C_{19}H_{16}N_2OS_2$ requires C, 64.74; H, 4.58; N, 7.95%]; δ_H (300 MHz; $CDCl_3$) 1.60–1.68 (2H, m, 6-CH_2), 1.92–2.06 (2H, m, 5-CH_2), 2.49–2.57 (1H, m, 7-CH_2), 2.63–2.70 (1H, m, 7-CH_2), 4.17 (1H, s, 4-C*H*), 5.19 (2H, s, NH_2), 6.80–7.20 (6 H, m, Ar*H*), 7.26 (1H, s, C=C*H*); δ_C (75 MHz, $CDCl_3$) 21.8, 27.1, 27.2, 38.6, 60.8, 114.9, 116.0, 125.1, 126.2, 126.8, 127.1, 128.5, 140.2, 141.3, 147.6, 158.8.

5.1.7. 2-Amino-4-(2-furyl)-8-[(*E*)-2-furylmethylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4l)

White solid, yield 98%, mp 193–195 °C; [found C, 71.29; H, 4.98; N, 8.80. $C_{19}H_{16}N_2O_3$ requires C, 71.24; H, 5.03; N, 8.74%]; δ_H (300 MHz; $CDCl_3$) 1.68–1.76 (2H, m, 6-CH_2), 2.08–2.11 (2H, m, 5-CH_2), 2.63–2.73 (1H, m, 7-CH_2), 2.83–2.92 (1H, m, 7-CH_2), 4.13 (1H, s, 4-C*H*), 4.59 (2H, s, NH_2), 6.62 (1H, s, C=C*H*), 6.18–7.42 (6 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 21.6, 27.0, 27.2, 37.5, 57.2, 110.5, 111.0, 111.3, 119.8, 126.8, 141.8, 142.8, 143.4, 152.9, 154.5, 159.7.

5.1.8. 2-Amino-4-(2,4-dichlorophenyl)-8-[(*E*)-(2,4-dichloro-phenyl)methylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4m)

White solid, yield 99%, mp 190–191 °C; [found C, 57.70; H, 3.29; N, 5.95. $C_{23}H_{16}Cl_4N_2O$ requires C, 57.77; H, 3.37; N, 5.86%]; δ_H (300 MHz; $CDCl_3$) 1.67–1.79 (2H, m, 6-CH_2), 1.93–2.03 (1H, m, 5-CH_2), 2.16–2.25 (1H, m, 5-CH_2), 2.52–2.55 (1H, m, 7-CH_2), 2.61–2.68 (1H, m, 7-CH_2), 4.78 (1H, s, 4-C*H*), 4.83 (2H, s, NH_2), 6.97 (1H, s, C=C*H*), 7.32–7.55 (6 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 22.0, 26.9, 27.0, 39.0, 58.5, 115.4, 119.2, 119.4, 126.6, 128.0, 129.3, 131.1, 131.2, 133.3, 133.5, 133.6, 134.1, 134.7, 138.7, 141.5, 159.4.

5.1.9. 2-Amino-4-[4-(dimethylamino)phenyl]-8-(*E*)-[4-(dimethylamino)phenyl]methylid-ene-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4n)

White solid, yield 98%, mp 196–197 °C; [found C, 76.12; H, 7.00; N, 13.07. $C_{27}H_{30}N_4O$ requires C, 76.03; H, 7.09; N, 13.13%]; δ_H (300 MHz; $CDCl_3$) 1.60–1.67 (2H, m, 6-CH_2), 1.90–2.03 (1H, m, 5-CH_2), 2.20–2.27 (1H, m, 5-CH_2), 2.59–2.67 (1H, m, 7-CH_2), 2.70–2.77 (1H, m, 7-CH_2), 2.89 (6 H, s, Ar-N(CH_3)$_2$), 2.94 (6 H, s, Ar-N(CH_3)$_2$), 3.90 (1H, s, 4-C*H*), 4.60 (2H, br s, NH_2), 6.69 (1H, s, C=C*H*), 6.61–7.00 (8 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 21.0, 27.1, 27.9, 39.1, 41.0, 40.7, 62.1, 111.0, 112.9, 114.8, 120.9, 121.6, 121.9, 128.7, 130.9, 132.3, 136.3, 144.4, 147.9, 150.9, 157.1.

5.1.10. 2-Amino-4-[(*E*)-2-phenylethenyl]-8-[(*E*,2*E*)-3-phenyl-2-propenylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4o)

White solid, yield 99%, mp 159–161 °C; [found C, 82.69; H, 6.25; N, 7.05. $C_{27}H_{24}N_2O$ requires C, 82.62; H, 6.16; N, 7.14]; δ_H (300 MHz; $CDCl_3$) 1.70–1.76 (2H, m, 6-CH_2), 2.03–2.10 (1H, m, 5-CH_2), 2.22–2.26 (1H, m, 5-CH_2), 2.65–2.70 (1H, m, 7-CH_2), 2.75–2.80 (1H, m, 7-CH_2), 3.58 (1H, d, J = 9.0 Hz, 4-C*H*), 4.61 (2H,

br s, NH_2), 5.80–7.31 (15 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 21.8, 26.1, 27.1, 40.5, 60.2, 112.5, 120.9, 121.1, 123.6, 124.6, 125.5, 126.9, 127.9, 128.4, 128.6, 128.9, 129.9, 132.9, 136.7, 137.1, 138.4, 141.5, 159.8.

5.1.11. 2-Amino-4-(1-naphthyl)-8-[(*E*)-1-naphthyl-methylidene]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4p)

White solid, yield 99%, mp 201–202 °C; [found C, 84.55; H, 5.55; N, 6.41. $C_{31}H_{24}N_2O$ requires C, 84.52; H, 5.49; N, 6.36]; δ_H (300 MHz; $CDCl_3$) 1.48–1.59 (2H, m, 6-CH_2), 1.79–2.06 (2H, m, 5-CH_2), 2.38–2.45 (1H, m, 7-CH_2), 2.52–2.60 (1H, m, 7-CH_2), 4.63 (2H, s, NH_2), 4.90 (1H, br s, 4- C*H*), 7.39 (1H, s, C=C*H*), 7.37–8.30 (14 H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 22.3, 27.3, 27.5, 28.8, 60.5, 116.1, 120.0, 122.9, 124.8, 124.9, 125.0, 125.7, 125.9, 126.0, 126.3, 126.5, 127.0, 127.5, 128.1, 128.9, 129.0, 131.0, 131.7, 132.0, 133.1, 133.6, 134.2, 135.4, 138.3, 141.6, 159.3.

5.2. General procedure for the synthesis of 1,2,4-oxadiazoles 5 and 6

The 4*H*-pyran (**3** or **4**, 1 mmol) and *N*-hydroxyaryl-carboximidoyl chloride (1 mmol) were dissolved in benzene (15 mL). A solution of triethylamine (1 mmol) in benzene (2 mL) was added drop-wise to the above mixture and refluxed for 5 h. Then the triethylamine hydrochloride was filtered off, the solvent removed in vacuo and the residue purified by a column with silica gel using petroleum ether/ethyl acetate (9:1 v/v) mixture to obtain pure 1,2,4-oxadiazoles **5** and **6**.

5.2.1 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-6-methyl-4-phenyl-8-[(*E*)-phenylmethylidene]-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-amine (5a)

White solid, yield 56%, mp 180–182 °C; [found: C, 70.73; H, 4.90; N, 11.07. $C_{30}H_{25}ClN_4O_2$ requires C, 70.79; H, 4.95; N, 11.01]; δ_H (300 MHz, $CDCl_3$) 2.29 (3H, s, N-CH_3), 2.85 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.13 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.41 (1H, d, *J* 14.5 Hz, 7-CH_2), 3.61 (1H, d, *J* 14.8 Hz, 7-CH_2), 4.41 (1H, s, 4-CH), 6.53 (2H, br s, NH_2), 6.91 (1H, s, C=CH), 7.17–7.93 (14 H, m, Ar-H).

5.2.2. 4-(4-Chlorophenyl)-8-[(*E*)-(4-chlorophenyl)-methylidene]-3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-ylamine (5b)

White solid, yield 61%, mp 197–199 °C; [found: C, 62.40; H, 4.08; N, 9.77. $C_{30}H_{23}Cl_3N_4O_2$ requires C, 62.35; H, 4.01; N, 9.70]; δ_H (300 MHz, $CDCl_3$) 2.34 (3H, s, N-CH_3), 2.93 (1H, d, *J* 16.2Hz, 5-CH_2), 3.25 (1H, d, *J* 16.2 Hz, 5-CH_2), 3.51 (1H, d, *J* 14.1 Hz, 7-CH_2), 3.67 (1H, d, *J* 14.1 Hz, 7-CH_2), 4.39 (1H, s, 4-CH), 6.64 (2H, br s, NH_2), 6.97 (1H, s, C=CH), 7.14–8.02 (12H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 40.1, 43.7, 53.6, 54.2, 73.6, 113.5, 122.6, 126.1, 126.7, 127.2, 128.1, 128.6, 128.8, 129.4, 129.7, 130.3, 130.8, 132.8, 133.2, 134.4, 139.5, 142.2, 156.4, 166.7, 175.6.

5.2.3. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-6-methyl-4-(4-methylphenyl)-8-[(*E*)-(4-methylphenyl)methylidene]-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-amine (5c)

Viscous liquid, yield 59%, [found: C, 71.47; H, 5.48; N, 10.49. $C_{32}H_{29}ClN_4O_2$ requires C, 71.57; H, 5.44; N, 10.43]; δ_H (300 MHz, $CDCl_3$) 2.27 (3H, s, Ar-CH_3), 2.28 (3H, s, Ar-CH_3), 2.36 (3H, s, N-CH_3), 2.86 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.11 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.40 (1H, d, *J* 13.5 Hz, 7-CH_2), 3.61 (1H, d, *J* 13.5 Hz, 7-CH_2), 4.37 (1H, s, 4-CH), 6.53 (2H, br s, NH_2), 6.95 (1H, s, C=CH), 7.07–8.01 (12H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.0, 21.2, 40.3, 44.3, 54.4, 55.1, 74.4, 114.0, 122.8, 126.0, 127.3, 127.4, 127.9, 128.1, 128.6, 129.0, 129.1, 129.3, 129.8, 130.7, 133.4, 136.6, 137.1, 139.6, 140.9, 156.5, 159.7, 166.7, 176.0.

5.2.4. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(4-methoxyphenyl)-8-[(*E*)-(4-methoxyphenyl)methylidene]-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-amine (5d)

White solid, yield 50%, mp 190–192 °C; [found: C, 67.46; H, 5.10; N, 9.95. $C_{32}H_{29}ClN_4O_4$ requires C, 67.54; H, 5.14; N, 9.85]; δ_H (300 MHz, $CDCl_3$) 2.31 (3H, s, N-CH_3), 2.92 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.21 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.45 (1H, d, *J* 14.1 Hz, 7-CH_2), 3.70 (1H, d, *J* 14.1 Hz, 7-CH_2), 3.76 (3H, s, Ar-OCH_3), 3.84 (3H, s, Ar-OCH_3), 4.35 (1H, s, 4-CH), 6.53 (2H, br s, NH_2), 6.97 (1H, s, C=CH), 6.81–7.97 (12H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 39.8, 43.9, 54.0, 54.5, 55.2, 55.3, 113.8, 113.9, 122.9, 124.4, 125.9, 128.5, 128.6, 128.9, 129.0, 130.5, 135.9, 136.7, 139.4, 156.5, 158.6, 158.8, 176.1.

5.2.5. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(2-methylphenyl)-8-[(*E*)-(2-methylphenyl)methylidene]-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-amine (5e)

White solid, yield 47%, mp 193–194 °C; [found: C, 71.66; H, 5.38; N, 10.48. $C_{32}H_{29}ClN_4O_2$ requires C, 71.57; H, 5.44; N, 10.43]; δ_H (300 MHz, $CDCl_3$) 2.24 (3H, s, Ar-CH_3), 2.30 (3H, s, Ar-CH_3), 2.38 (3H, s, N-CH_3), 2.75 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.11 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.40 (1H, d, *J* 14.5 Hz, 7-CH_2), 3.61 (1H, d, *J* 14.5 Hz, 7-CH_2), 4.56 (1H, s, 4-CH), 6.60 (2H, br s, NH_2), 6.98 (1H, s, C=CH), 7.10–8.00 (12H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 20.9, 21.1, 40.1, 43.8, 53.9, 54.8, 73.9, 114.3, 122.6, 126.4, 127.0, 127.2, 127.7, 128.0, 128.8, 129.0, 129.2, 129.3, 130.0, 130.8, 133.0, 136.8, 137.6, 139.8, 141.0, 156.9, 160.0, 166.1, 175.8.

5.2.6. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(2-methoxyphenyl)-8-[(*E*)-(2-methoxyphenyl)methylidene]-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-amine (5f)

White solid, yield 45%, mp 200–201 °C; [found: C, 67.64; H, 5.06; N, 9.74. $C_{32}H_{29}ClN_4O_4$ requires C, 67.54; H, 5.14; N, 9.85]; δ_H (300 MHz, $CDCl_3$) 2.25 (3H, s, N-CH_3), 2.88 (1H, d, *J* 15.6 Hz, 5-CH_2), 3.19–3.31 (2H, m, 5-CH_2 and 7-CH_2), 3.49 (1H, d, *J* 14.1 Hz, 7-CH_2), 3.86 (3H, s, Ar-OCH_3), 3.93 (3H, s, Ar-OCH_3), 5.00 (1H, s, 4-CH), 6.56 (2H, br s, NH_2), 6.89–7.96 (13H, m, Ar-H).

5.2.7. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(3-fluorophenyl)-8-[(*E*)-(3-fluorophenyl)methylidene]-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-amine (5g)

White solid, yield 65%, mp 183–184 °C; [found: C, 66.05; H, 4.17; N, 10.20. $C_{30}H_{23}ClF_2N_4O_2$ requires C, 66.12; H, 4.25; N, 10.28]; δ_H (300 MHz, $CDCl_3$) 2.31 (3H, s, N-CH_3), 2.85 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.12 (1H, d, *J* 15.9 Hz, 5-CH_2), 3.39 (1H, d, *J* 14.8 Hz, 7-CH_2), 3.57 (1H, d, *J* 14.8 Hz, 7-CH_2), 4.42 (1H, s, 4-CH), 6.56 (2H, br s, NH_2), 6.94 (1H, s, C=CH), 6.87–7.97 (12H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 40.6, 44.9, 54.5, 55.3, 73.6, 113.9, 115.0, 115.7, 121.6, 123.7, 124.9, 125.8, 128.1, 128.6, 129.0, 129.8, 130.0, 136.9, 139.6, 146.5, 156.7, 166.0, 175.9.

5.2.8. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(2,4-dichlorophenyl)-8-[(*E*)-(2,4-dichlorophenyl)methylidene]-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-amine (5h)

White solid, yield 40%, mp 208–209 °C; [found: C, 55.77; H, 3.35; N, 8.60. $C_{30}H_{21}Cl_5N_4O_2$ requires C, 55.71; H, 3.27; N, 8.66]; δ_H (300 MHz, $CDCl_3$) 2.28 (3H, s, N-CH_3), 2.81 (1H, d, *J* 12.3 Hz, 5-CH_2), 3.18–3.25 (2H, m, 5-CH_2 and 7-CH_2), 3.37 (1H, d, *J* 16.2 Hz, 7-CH_2), 5.06 (1H, s, 4-CH), 6.62 (2H, br s, NH_2), 6.95 (1H, s, C=CH), 7.08–7.96 (10H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 37.5, 44.8, 54.4, 54.7, 73.6, 113.9, 119.0, 125.6, 126.7, 127.9, 128.5,

128.8, 128.9, 129.2, 129.5, 131.0, 132.9, 133.2, 133.7, 133.9, 134.7, 136.8, 139.4, 157.0, 165.9, 175.6.

5.2.9. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-[4-(dimethylamino)phenyl]-8-(*E*)-[4-(dimethylamino)phenyl]-methylidene-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-2-amine (5i)

Dark brown solid, yield 50%, mp 179–180 °C; [found: C, 68.69; H, 5.84; N, 14.20. $C_{34}H_{35}ClN_6O_2$ requires C, 68.62; H, 5.93; N, 14.12]; δ_H (300 MHz, $CDCl_3$) 2.31 (3H, s, N-CH_3), 2.88 (6H, s, Ar-N-$(CH_3)_2$), 2.95–3.00 (7H, m, Ar-N-$(CH_3)_2$ and 5-CH_2), 3.18 (1H, d, *J* 15.3 Hz, 5-CH_2), 3.24 (1H, d, *J* 13.8 Hz, 7-CH_2), 3.50 (1H, d, *J* 13.8 Hz, 7-CH_2), 4.28 (1H, s, 4-CH), 6.50 (2H, br s, NH_2), 6.92 (1H, s, C=CH), 6.63–7.96 (12H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 39.6, 40.2, 40.5, 44.1, 54.4, 54.8, 74.6, 111.8, 112.5, 122.8, 124.2, 126.0, 128.5, 128.6, 128.8, 130.4, 131.9, 136.5, 139.5, 149.4, 149.5, 156.6, 165.7, 176.3.

5.2.10. 4-(4-Chlorophenyl)-8-[(*E*)-(4-chlorophenyl)-methylidene]-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4*H*-chromen-2-ylamine (6a)

Viscous liquid, yield 40%, [found: C, 68.11; H, 4.30; N, 7.85. $C_{30}H_{23}Cl_2N_3O_2$ requires C, 68.19; H, 4.39; N, 7.95]; δ_H (300 MHz, $CDCl_3$) 1.58–1.75 (2H, m, 6-CH_2), 1.98–2.26 (2H, m, 5-CH_2), 2.55–2.59 (1H, m, 7-CH_2), 2.66–2.71 (1H, m, 7-CH_2), 4.35 (1H, s, 4-CH), 6.54 (2H, s, NH_2), 6.91 (1H, s, C=CH), 7.23–8.04 (13H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 22.3, 27.0, 27.5, 42.3, 73.9, 117.5, 121.2, 127.3, 128.4, 128.6, 128.7, 128.9, 129.5, 130.2, 130.5, 130.8, 132.5, 132.6, 135.6, 141.2, 143.1, 156.7, 166.8, 175.8.

5.2.11. 4-(4-Methoxyphenyl)-8-[(*E*)-(4-methoxyphenyl)-methylidene]-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4*H*-chromen-2-ylamine (6b)

White solid, yield 52%, mp 145–147 °C; [found: C, 73.86; H, 5.71; N, 8.01. $C_{32}H_{29}N_3O_4$ requires C, 73.97; H, 5.63; N, 8.09]; δ_H (300 MHz, $CDCl_3$) 1.53–1.74 (2H, m, 6-CH_2), 2.01–2.18 (2H, m, 5-CH_2), 2.55–2.64 (1H, m, 7-CH_2), 2.69–2.78 (1H, m, 7-CH_2), 3.76 (Ar-OCH_3), 3.84 (Ar-OCH_3), 4.31 (1H, s, 4-CH), 6.48 (2H, s, NH_2), 6.91 (1H, s, C=CH), 6.80–8.04 (13H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 22.4, 27.1, 27.4, 41.8, 55.1, 55.2, 74.6, 113.5, 113.7, 117.1, 121.4, 127.2, 127.5, 128.3, 128.5, 129.1, 129.8, 130.5, 130.6, 136.8, 141.1, 156.6, 158.2, 158.3, 166.6.

5.2.12. 4-(4-Fluorophenyl)-8-[(*E*)-(4-fluorophenyl)-methylidene]-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4*H*-chromen-2-ylamine (6c)

White solid, yield 51%, mp 96–98 °C; [found: C, 72.80; H, 4.76; N, 8.39. $C_{30}H_{23}F_2N_3O_2$ requires C, 72.72; H, 4.68; N, 8.48]; δ_H (300 MHz, $CDCl_3$) 1.58–1.72 (2H, m, 6-CH_2), 1.99–2.20 (2H, m, 5-CH_2), 2.52–2.60 (1H, m, 7-CH_2), 2.65–2.72 (1H, m, 7-CH_2), 4.36 (1H, s, 4-CH), 6.51 (2H, s, NH_2), 6.92 (1H, s, C=CH), 6.94–8.04 (13H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 22.4, 27.0, 27.5, 42.1, 74.3, 115.1, 115.3, 117.5, 121.2, 127.3, 127.4, 128.7, 129.6, 129.7, 130.8, 130.9, 133.1, 133.2, 140.3, 141.1, 156.7, 166.8, 176.0.

5.2.13. 4-(2-Methylphenyl)-8-[(*E*)-(2-methylphenyl)-methylidene]-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4*H*-chromen-2-ylamine (6d)

Viscous liquid, yield 47%, [found: C, 78.89; H, 6.06; N, 8.51. $C_{32}H_{29}N_3O_2$ requires C, 78.82; H, 5.99; N, 8.62]; δ_H (300 MHz, $CDCl_3$) 1.57–1.79 (2H, m, 6-CH_2), 1.96–2.29 (2H, m, 5-CH_2), 2.34 (Ar-CH_3), 2.41–2.56 (1H, m, 7-CH_2), 2.65 (Ar-CH_3), 2.65–2.79 (1H, m, 7-CH_2), 4.71 (1H, s, 4-CH), 6.56 (2H, s, NH_2), 6.97 (1H, s, C=CH), 7.06–8.25 (13H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 19.8, 20.2, 22.5, 27.1, 27.2, 42.3, 74.3, 117.8, 121.2, 125.4, 126.5, 126.9, 127.3, 127.5, 128.2, 128.3, 128.7, 128.9, 129.3, 129.9, 130.2, 130.6, 130.7, 136.4, 136.8, 140.7, 157.1, 166.7, 176.2.

5.2.14. 4-(2-Methoxyphenyl)-8-[(*E*)-(2-methoxyphenyl)-methylidene]-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4*H*-chromen-2-ylamine (6e)

Viscous liquid, yield 41%, [found: C, 74.04; H, 5.52; N, 8.17. $C_{32}H_{29}N_3O_4$ requires C, 73.97; H, 5.63; N, 8.09]; δ_H (300 MHz, $CDCl_3$) 1.59–1.72 (2H, m, 6-CH_2), 2.02–2.18 (2H, m, 5-CH_2), 2.46–2.57 (1H, m, 7-CH_2), 2.69–2.79 (1H, m, 7-CH_2), 3.89 (Ar-OCH_3), 3.94 (Ar-OCH_3), 5.01 (1H, s, 4-CH), 6.55 (2H, s, NH_2), 7.02 (1H, s, C=CH), 6.86–8.04 (13H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 22.5, 26.9, 27.4, 34.5, 55.4, 56.1, 73.6, 110.2, 111.0, 116.9, 117.8, 119.9, 120.9, 126.1, 127.3, 127.6, 128.1, 128.6, 128.9, 129.4, 130.2, 130.3, 130.6, 133.5, 140.9, 157.2, 157.3, 157.6, 166.6, 176.2.

5.2.15. 4-(3-Fluorophenyl)-8-[(*E*)-(3-fluorophenyl)-methylidene]-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4*H*-chromen-2-ylamine (6f)

White solid, yield 55%, mp 166–168 °C; [found: C, 72.64; H, 4.60; N, 8.56. $C_{30}H_{23}F_2N_3O_2$ requires C, 72.72; H, 4.68; N, 8.48]; δ_H (300 MHz, $CDCl_3$) 1.61–1.73 (2H, m, 6-CH_2), 2.02–2.22 (2H, m, 5-CH_2), 2.54–2.63 (1H, m, 7-CH_2), 2.68–2.77 (1H, m, 7-CH_2), 4.39 (1H, s, 4-CH), 6.53 (2H, s, NH_2), 6.93 (1H, s, C=CH), 6.85–8.04 (13H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 22.3, 27.0, 27.5, 42.7, 73.9, 113.6, 114.1, 115.0, 116.0, 117.7, 121.4, 123.9, 125.0, 127.3, 128.7, 129.5, 129.8, 130.7, 129.3, 141.1, 147.1, 156.7, 164.7, 166.8, 175.8.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.04.033.

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