Efficient synthesis of 4*H*-benzo[*d*][1,3]oxazin-4-ones from anthranilic acids and aryl isoselenocyanates

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A synthesis in good to excellent yields of 23 4*H*-benzo[*d*][1,3]oxazin-4-ones, 18 of which are novel, from monosubstituted anthranilic acids and variously substituted phenyl isoselenocyanates without using any harsh reagents has been developed. The Se powder precipitated during the reaction could be efficiently recycled for the preparation of the aryl isoselenocyanates.

Keywords: benzoxazinone, aryl isoselenocyanate, anthranilic acid, cyclisation, selenium powder

4*H*-Benzo[*d*][1,3]oxazin-4-ones are alternative substrate inhibitors of the serine proteinase human leukocyte elastase,[1] as well as novel specific PSA (puromycin-sensitive aminopeptidase) inhibitors to the invasion of tumour cells that are more stable than the traditional ones.[2] 4*H*-Benzo[*d*][1,3]oxazin-4-one derivatives play an important role in the defence of the human body against infections[3] and show anti-cancer effects.[4] In addition, 4*H*-benzo[*d*][1,3]oxazin-4-ones are widely used as intermediates to prepare various biologically important compounds.[5–8] Thus, a variety of methods for the synthesis of 4*H*-benzo[*d*][1,3]oxazin-4-ones have been reported.

The three ways of synthesising of 2-(arylamino)-4*H*-benzo[*d*][1,3]oxazin-4-ones, are as follows (Scheme 1): (1) methyl *N*-aryldithiocarbamates react with 5-substituted potassium anthranilates through a desulfurisation process;[9] (2) substituted methyl 2-aminobenzoates undergo a cyclisation with isocyanates;[1] and (3) a reaction of iminophosphoranes and aryl isocyanates *via* tetrabutylammonim fluoride-mediated cyclisation.[10] However, HgO used as a desulfurising reagent in method (1) is a highly toxic compound which is harmful to the environment and methods (2) and (3) often give low yields that limit their application.

Isoselenocyanates are widely used in chemistry for preparing selenium-containing compounds as well as non-selenium-containing compounds because of their low toxicity, relative stability and excellent reactivity.[11–16] Although there are many reports of the preparation of selenium-containing derivatives,[12,13,15–17] only a few papers focus on the synthesis of non-selenium-containing compounds.[11,18] Thus, inspired by the reported cyclodeselenization reactions, we have designed a convenient method to obtain a series of non-selenium-containing compounds, 2-(arylamino)-4*H*-benzo[*d*][1,3]oxazin-4-ones from various aryl isoselenocyanates and 2-aminobenzoic acids *via* a cyclodeselenisation reaction.

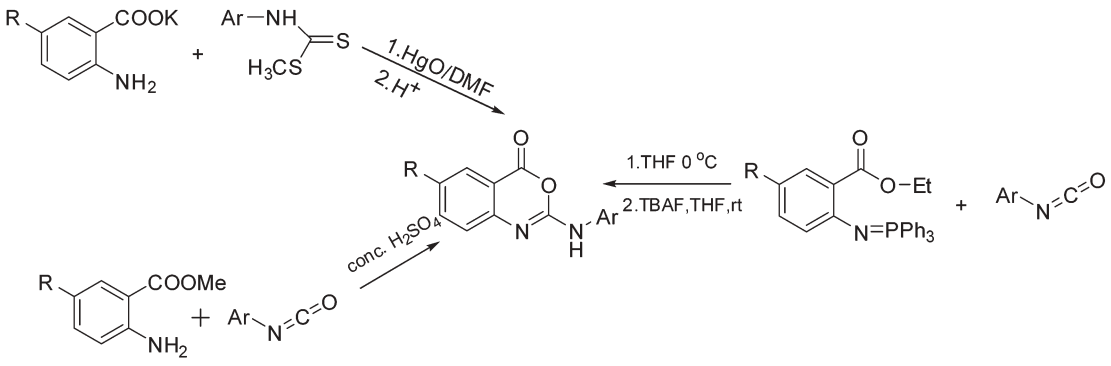
Results and discussion

4-Methoxyphenyl isoselenocyanate and 2-aminobenzoic acid were chosen as the candidates to optimise the reaction conditions for the cyclisation reaction (Scheme 2), and the results are summarised in Table 1.

The effects of different solvents, reaction duration and temperature, and the amount of 2-aminobenzoic acid on the efficiency of the cyclisation reaction of 1 equiv. 4-methoxyphenyl isoselenocyanate were investigated. It was clear that DMF (Table 1, entry 7) was the optimal solvent while others such as pyridine, THF, EtOAc and EtOH gave lower yields (Table 1, entries 1–4). Moreover, toluene and CH_2Cl_2 gave no desired product (Table 1, entries 5 and 6). To optimise the duration and temperature of the reaction, the reaction was carried out at times ranging from 4.5 to 24h and at temperatures ranging from 40 to 80 °C. However, in DMF as solvent 4.5h was found to be sufficient time to attain a 94% yield and an increase of reaction temperature above 40 °C did not improve the yield, which was probably due to side reactions. Furthermore, the effect of the amount of 2-aminobenzoic acid was taken into consideration and it was found that as little as 1.1 equiv. was optimal to ensure a high reaction yield.

On the basis of these results, the optimal conditions for the efficient (94% yield) cyclisation reaction of 1 equiv. of 4-methoxyphenyl isoselenocyanate were heating with 1.1 equiv. 2-aminobenzoic acid in DMF at 40 °C for 4.5h (Table 1, entry 10). The scope of this method was then evaluated using variously substituted phenyl isoselenocyanates **1** in reaction with 2-amino-, 2-amino-4-chloro, and 2-amino-3-methyl-benzoic acid **2** to obtain 2-(arylamino)-4*H*-benzo[*d*][1,3]oxazin-4-ones **3** (Scheme 3). The yields obtained for all 23 cyclisations, which were good to excellent, are shown in Table 2.

The five known compounds **3l–p** were characterised by comparison of their physical and spectral properties with



Scheme 1 Three synthetic routes to 4*H*-benzo[*d*][1,3]oxazin-4-ones.

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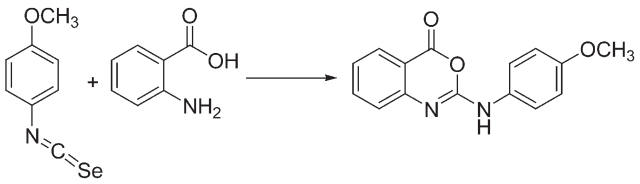


Scheme 2

Table 1 Optimisation of reaction conditions for the cyclisation reaction of 1 equiv. 4-methoxyphenyl isoselenocyanate and 2-aminobenzoic acid (see Scheme 2)

Entry	2-Aminobenzoic acid/equiv.	Solvent	Temp /°C	Time /h[a]	Yield /%[b]
1	1	Pyridine	60	6	75
2	1	THF	60	6	71
3	1	EtOAc	60	6	62
4	1	EtOH	60	6	83
5	1	Toluene	60	12	None
6	1	CH_2Cl_2	Reflux	24	None
7	1	DMF	40	4.5	93
8	1	DMF	60	4.5	91
9	1	DMF	80	4.5	86
10	1.1	DMF	40	4.5	94
11	1.3	DMF	40	4.5	94

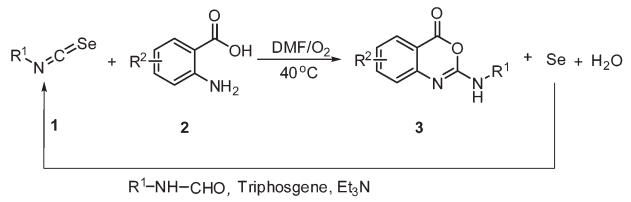
[a] Reactions were monitored by TLC(petroleum ether/ethyl acetate, 10:1).
[b] Isolated yield based on isoselenocyanate.

literature data.[9,19] The 18 new compounds **3a–k**, **q–w**, which all had similar structures to **3l–p** showed very similar IR, ^{1}H NMR and ^{13}C NMR spectral properties and, together with HRMS data, were easily characterised.

From Table 2, it is clear that the nature of R^1 group on the isoselenocyanates greatly affected the reaction yields. Aryl isoselenocyanates containing electron-withdrawing groups reacted with 2-amino-3-methylbenzoic acid gave higher yields than those containing electron-donating groups (Table 2, entries 1–9). Also, the position of the substituent on the R^1 group had an impact on the yields. The *para*- and *ortho*-substituted aryl isoselenocyanates gave higher yields than the corresponding *meta*-substituted analogues when they reacted with the same 2-aminobenzoic acid (Table 2, entries 7, 8, 13 and 14). In order to widen the scope of the reaction, 2-aminobenzoic acid and 2-amino-4-chlorobenzoic acid were also investigated. Unsubstituted 2-aminobenzoic acid gave a slightly better yield than 2-amino-3-methylbenzoic acid and 2-amino-4-chlorobenzoic acid (Table 2, entries 6, 12 and 20). From the results in Table 2, it was also clear that 1-naphthyl isoselenocyanate had good reactivity either with 2-amino-3-methylbenzoic acid (entry 11) or with 2-aminobenzoic acid (entry 17). An alkyl isoselenocyanate was treated with 2-amino-4-chlorobenzoic acid (entry 24), but no product resulted.

It should be noted that the Se powder formed during the reaction could be filtered off and used to prepare aryl isoselenocyanates without any loss in reactivity.[11] For example, 2-(4-chlorophenylamino)-8-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**3b**) and 8-methyl-2-(4-tolylamino)-4*H*-benzo[*d*][1,3]-oxazin-4-one (**3h**) were obtained in yields of 97 and 78% (Table 2, entries 2 and 8, respectively) by using the aryl isoselenocyanates, **1b** and **1h**, prepared from recovered selenium.

A plausible mechanism is proposed for the formation of 4*H*-benzo[*d*][1,3]oxazin-4-ones (Scheme 4). Firstly, 2-selenoureidobenzoic acid **3–1** was generated from aryl isoselenocyanate **1** and 2-aminobenzoic acid **2**, which then underwent an intramolecular cyclisation and produced the intermediate **3–2**. Finally, with the help of oxygen, the intermediate **3–2** converted to 4*H*-benzo[*d*][1,3]oxazin-4-one **3** via cyclodeselenisation.



Scheme 3

Table 2 Synthesis of 2-(arylamino)-4*H*-benzo[*d*][1,3]oxazin-4-ones (see Scheme 3)

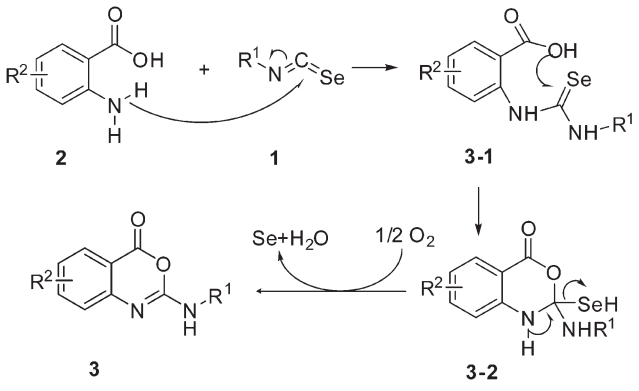
Entry	**1** (R^1)	**2** (R^2)	Product	Yield/%[a]
1	4-FC_6H_4	3-Me	**3a**	96
2	4-ClC_6H_4	3-Me	**3b**	98,97[b]
3	4-BrC_6H_4	3-Me	**3c**	95
4	4-$MeOC_6H_4$	3-Me	**3d**	89
5	4-$EtOC_6H_4$	3-Me	**3e**	84
6	C_6H_5	3-Me	**3f**	80
7	3-MeC_6H_4	3-Me	**3g**	72
8	4-MeC_6H_4	3-Me	**3h**	79,78[b]
9	2-EtC_6H_4	3-Me	**3i**	74
10	3,5-MeC_6H_3	3-Me	**3j**	52
11	1-Naphthyl	3-Me	**3k**	84
12	C_6H_5	H	**3l**	87
13	2-MeC_6H_4	H	**3m**	83
14	3-MeC_6H_4	H	**3n**	80
15	4-$MeOC_6H_4$	H	**3o**	94
16	2,5-ClC_6H_3	H	**3p**	75
17	1-Naphthyl	H	**3q**	90
18	4-$MeOC_6H_4$	4-Cl	**3r**	80
19	4-$EtOC_6H_4$	4-Cl	**3s**	75
20	C_6H_5	4-Cl	**3t**	72
21	2-EtC_6H_4	4-Cl	**3u**	64
22	3-MeC_6H_4	4-Cl	**3v**	63
23	4-MeC_6H_4	4-Cl	**3w**	69
24	C_4H_9	4-Cl	None	none

[a] Isolated yields based on aryl isoselenocyanates.
[b] Using aryl isoselenocyanates prepared from recycled selenium powder.

In conclusion, an efficient, mild and environmentally friendly synthesis of 4*H*-benzo[*d*][1,3]oxazin-ones was developed *via* cyclodeselenization of readily available aryl isoselenocyanates and 2-aminobenzoic acids. A series of 4*H*-benzo[*d*][1,3]oxazin-ones was obtained in good to excellent yields. In addition, the Se powder formed during the reaction could be recycled for preparation of the aryl isoselenocyanates.

Experimental

NMR spectra were obtained on a Varian 400 spectrometer (^{1}H NMR at 400MHz, and ^{13}C NMR at 100 MHz) in $CDCl_3$ or DMSO-d_6 using



Scheme 4 Plausible mechanism for the formation of 2-(arylamino)-4*H*-benzo[*d*] [1,3]oxazin-4-ones.

TMS as internal standard. Mass spectra (ESI-MS) were determined on a Thermo Finigan LCQ-Advantage. High resolution electrospray mass spectra (ESI-HRMS) were determined on an Agilent 6210 TOF instrument. Electron impact (EI)-mass spectra (MS) were determined on a Thermo Finnigan Trace DSQ instrument. High resolution EI-mass spectra (EI-HRMS) were recorded on a Waters GCT Premier instrument. Melting points were measured on a Büchi B-540 capillary melting point apparatus. IR spectra were recorded in KBr discs on a Nicolet Avatar-370 spectrometer. The three 2-aminobenzoic acids and all solvents were available commercially. Formanilides were prepared from phenylamine,[20] and aryl isoselenocyanate were prepared by Fernández-Bolaños's method.[11]

Synthesis of aryl isoselenocyanates

A solution of 2-ethylaniline (25 mmol) and HCOOH (25 mmol) in toluene (50 mL) was heated to reflux for 3h. Then the reaction mixture was cooled to 0 °C and reacted with Et_3N (75 mmol), Se powder (35 mmol) and toluene containing triphosgene (25 mmol) for 30 min, then the reaction was heated to reflux for 18h. After completion, the reaction mixture was filtered and the combined filtrates were concentrated in *vacuo* to give a residue which was purified by column chromatography (petroleum ether/ethyl acetate, 10:1) to afford **1u** a transparent liquid (3.78 g, 83%).

1-Isoselenocyanato-2-methylbenzene (**1m**): White solid; m.p. 31.4–32.7 °C (lit.[21] 31–32 °C); IR: ν_{max} = 3021, 2885, 2119, 2071, 1606, 1589, 1484, 1458, 1380, 1114, 1038, 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.21–7.15 (m, 4H), 2.38 (s, 3H) ppm.

1-Isoselenocyanato-4-methylbenzene (**1h**): White solid; m.p. 59.8–61.9 °C (lit.[21] 66–68 °C); IR: ν_{max} = 3026, 2913, 2154, 2068, 1897, 1641, 1574, 1499, 1442, 1376, 1208, 856 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.15 (d, *J*=2.4 Hz, 4H), 2.35 (s, 3H) ppm.

1-Ethyl-2-isoselenocyanatobenzene (**1u**): Transparent liquid; IR: ν_{max} = 3069, 2967, 2931, 2872, 2111, 2061, 1597, 1574, 1482, 1449, 1375, 857, 788, 752, 625 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27–7.21 (m, 3H), 7.19–7.15 (m, 1H), 2.74 (q, 2H, *J* = 7.6 Hz), 1.26 (t,3H, *J* = 7.6 Hz) ppm.

1-Isoselenocyanato-4-methoxybenzene (**1d**): White solid; m.p. 48–51 °C (lit.[21] 43–44 °C); IR: ν_{max} = 2993, 2956, 2834, 2128, 2059, 1877, 1598, 1579, 1504, 1453, 1422, 1251, 1033, 853, 823 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.21 (d, *J* = 7.2 Hz, 2H), 6.84 (d, *J* = 7.2 Hz, 2H), 3.81 (s, 3H) ppm.

1-Isoselenocyanato-3,5-dimethylbenzene (**1j**): White solid; m.p. 30.4–31.6 °C; IR: ν_{max} = 2916, 2118, 2087, 1604, 1589, 1467, 1377, 1298, 1037, 844, 701 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.94 (s, 1H),6.90 (s, 2H), 2.29 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$): δ 139.2, 129.8, 129.0, 128.0, 123.5, 21.1 ppm; MS (EI): *m/z* (%) = 211 (M^+,100), 209 (50); HRMS-EI: Calcd for C_9H_9NSe 210.9900; found: 210.9905.

1-Fluoro-4-isoselenocyanatobenzene (**1[a]**): White solid; m.p. 45.8–47.7 °C; IR: ν_{max} = 3070, 2132, 1887, 1643, 1595, 1501, 1445, 1287, 1227, 1211, 1152, 1093, 1010, 862, 833, 778 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.28–7.24 (m, 2H), 7.07–7.03 (m, 2H) ppm.

1-Chloro-4-isoselenocyanatobenzene (**1b**): White solid; m.p. 70.3–73.2 °C (lit.[21] 70.5–71.5 °C); IR: ν_{max} = 3076, 2144, 2059, 1887, 1636, 1482, 1429, 1402, 1290, 1162, 1085, 1011, 849, 824, 469 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H) ppm.

1-Bromo-4-isoselenocyanatobenzene (**1c**): White solid; m.p. 80.5–82.0 °C; IR: ν_{max} = 3080, 2525, 2121, 2041, 1887, 1625, 1573, 1478, 1396, 1292, 1214, 1105, 1067, 844, 817, 657, 492 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.48 (d, *J* = 8.8 Hz, 2H),7.14 (d, *J* = 8.8 Hz, 2H) ppm.

1-Ethoxy-4-isoselenocyanatobenzene (**1e**): White solid; m.p. 95.4–97.8 °C; IR: ν_{max} = 2923, 2868, 2125, 1877, 1602, 1577, 1501, 1477, 1442, 1386, 1303, 1249, 1165, 1112, 1101, 1042, 923, 834, 821, 798 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.01 (q, *J* = 6.8 Hz, 2H), 1.41 (t, *J* = 6.8 Hz, 3H) ppm.

Synthesis of 4H-benzo[d][1,3]oxazin-ones; general procedure

Aryl isoselenocyanate (1 mmol) was added to a solution of a 2-aminobenzoic acid (1.1 mmol) in DMF (15 mL). The reaction mixture was heated at 40 °C for 4.5h. After the completion of the reaction, the reaction mixture was filtered and then washed with EtOAc (15 mL×2) to obtain Se powder. The combined filtrates were concentrated in *vacuo* and the residue was purified by column chromatography (petroleum ether/ethyl acetate, 10:1) to afford a white solid.

2-(4-Fluorophenylamino)-8-methyl-4H-benzo[d][1,3]oxazin-4-one (**3a**): White solid; m.p. 229.0–230.2 °C; IR: ν_{max} = 3283, 3101, 2923, 1743, 1656, 1567, 1510, 1483, 1322, 1269, 1213, 1161, 1102, 1063, 1028, 868, 825, 793, 756, 694 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.34 (s, 1H), 7.84–7.81 (m, 2H), 7.79–7.76 (m, 1H), 7.62–7.59 (m, 1H), 7.22–7.18 (m, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.1 (C=O), 157.5 ($^1J_{CF}$ = 237 Hz), 149.4, 147.4, 136.7, 134.4, 132.2, 125.3, 123.3, 120.4 ($^3J_{CF}$ = 7 Hz), 115.1 ($^2J_{CF}$ = 22 Hz), 113.3, 17.1 ppm; MS (ESI): *m/z* (%) = 269 (M^- -1,100); HRMS-ESI: Calcd for $C_{15}H_{10}FN_2O_2$ $(M-H)^-$ 269.0732; found: 269.0733.

2-(4-Chlorophenylamino)-8-methyl-4H-benzo[d][1,3]oxazin-4-one (**3b**): White solid; m.p. 262.5–263.7 °C; IR: ν_{max} = 3281, 3086, 2955, 1742, 1651, 1602, 1555, 1495, 1483, 1463, 1323, 1269, 1233, 1099, 1063, 1029, 1011, 818, 758, 695 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.45 (s, 1H), 7.86–7.84 (m, 2H), 7.82–7.80 (m, 1H), 7.66–7.64 (m, 1H), 7.44–7.42 (m, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 2.46 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.0 (C=O), 149.2, 147.2, 137.0, 136.7, 132.3, 128.3, 126.2, 125.3, 123.6, 120.2, 113.4, 17.1 ppm; MS (ESI): *m/z* (%) = 285 (M^--1,100), 287 (M^-+1, 33); HRMS-ESI: Calcd for $C_{15}H_{10}ClN_2O_2$ $(M-H)^-$ 285.0436; found: 285.0438.

2-(4-Bromophenylamino)-8-methyl-4H-benzo[d][1,3]oxazin-4-one (**3c**): White solid; m.p. 281.0–281.9 °C; IR: ν_{max} = 3280, 3084, 1741, 1652, 1602, 1554, 1491, 1463, 1323, 1269, 1234, 1062, 1028, 815, 758, 499, 491 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.46 (s, 1H), 7.81–7.78 (m, 3H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H,), 7.20 (t, *J* = 7.6 Hz, 1H), 2.45 (s, 3H,) ppm; ^{13}C NMR(DMSO-d_6): δ 159.0 (C=O), 149.2, 147.2, 137.4, 136.8, 132.4, 131.3, 125.4, 123.7, 120.7, 114.3, 113.5, 17.1 ppm; MS (ESI): *m/z* (%) = 329 (M^--1,100), 331 (M^-+1, 100); HRMS-ESI: Calcd for $C_{15}H_{10}BrN_2O_2$ $(M-H)^-$ 328.9931; found: 323.9938.

2-(4-Methoxyphenylamino)-8-methyl-4H-benzo[d][1,3]oxazin-4-one (**3d**): White solid; m.p. 206.9–207.5 °C; IR: ν_{max} = 3292, 3141, 2969, 1741, 1653, 1602, 1562, 1512, 1463, 1321, 1248, 1174, 1066, 1029, 817, 758, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.13 (s, 1H), 7.77–7.75 (m, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.95–6.93 (m, 2H), 3.74 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR(DMSO-d_6): δ 159.2 (C=O), 154.8, 149.6, 147.8, 136.6, 132.1, 131.0, 125.3, 123.0, 120.4, 113.7, 113.0, 55.1, 17.0 ppm; MS(ESI): *m/z*(%) = 281 (M^--1,100); HRMS-ESI: Calcd for $C_{16}H_{13}N_2O_3(M-H)^-$ 281.0932; found: 281.0929.

2-(4-Ethoxyphenylamino)-8-methyl-4H-benzo[d][1,3]oxazin-4-one (**3e**): White solid; m.p. 240.6–242.2 °C; IR: ν_{max} = 3292, 1759, 1738, 1637, 1598, 1513, 1461, 1324, 1293, 1222, 1182, 1053, 1029, 925, 863, 838, 811, 757, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.15 (s, 1H), 7.78 (d, *J* =7.2 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H) 7.61 (d, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.00 (q, *J* = 6.8 Hz, 2H), 2.42 (s, 3H), 1.32 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR(DMSO-d_6): δ 159.3, 154.0, 149.6, 147.9, 136.7, 132.1, 130.9, 125.4, 123.0, 120.3, 114.3, 113.1, 63.0, 17.1, 14.8 ppm; MS (ESI): *m/z* (%) = 295 (M^--1,100); HRMS-ESI: Calcd for $C_{17}H_{15}N_2O_3$ $(M-H)^-$ 295.1088; found: 295.1093.

8-Methyl-2-(phenylamino)-4H-benzo[d][1,3]oxazin-4-one (**3f**): White solid m.p. 216.4–218.5 °C; IR: ν_{max} = 3284, 3098, 2921, 1761, 1740, 1640, 1595, 1557, 1481, 1448, 1323, 1268, 1234, 1066, 1026, 756, 700 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.31 (s, 1H), 7.83–7.79 (m, 3H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 2.45 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.2 (C=O), 149.4, 147.5, 138.0, 136.7, 132.3, 128.5, 125.4, 123.4, 122.6, 118.8, 113.4, 17.1 ppm; MS (ESI): *m/z* (%) = 251 (M^--1, 100); HRMS-ESI: Calcd for $C_{15}H_{11}N_2O_2(M-H)^-$ 251.0826; found: 251.0828.

8-Methyl-2-(3-tolylamino)-4H-benzo[d][1,3]oxazin-4-one (**3g**): White solid; m.p. 205.2–206.9 °C; IR: ν_{max} = 3281, 3017, 2958, 1734, 1642, 1595, 1567, 1484, 1460, 1324, 1254, 1214, 1068, 773, 758, 689 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.16 (s, 1H), 7.73–7.71 (m, 1H), 7.65 (s, 1H), 7.57–7.53 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 2.42 (s, 3H), 2.30 (s, 3H) ppm; ^{13}C NMR(DMSO-d_6): δ 159.2 (C=O), 149.4, 147.6, 138.0, 137.6, 136.7, 132.3, 128.3, 125.4, 123.4, 123.3, 119.4, 116.0, 113.3, 21.4, 17.1 ppm; MS (ESI): *m/z* (%) = 265 (M^--1,100); HRMS-ESI: Calcd for $C_{16}H_{13}N_2O_2$ $(M-H)^-$ 265.0983; found: 265.0987.

8-Methyl-2-(4-tolylamino)-4H-benzo[d][1,3]oxazin-4-one (**3h**): White solid; m.p. 213.9–216.5 °C; IR: ν_{max} = 3290, 3086, 2918, 1761, 1738, 1731, 1641, 1613, 1598, 1550, 1456, 1325, 1266, 1235, 1062, 1030, 817, 757, 702 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.13 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 6.4 Hz, 1H), 7.10–7.05 (m, 3H), 2.39 (s, 3H), 2.25 (s, 3H) ppm; ^{13}C NMR(DMSO-d_6): δ 159.1 (C=O), 149.4, 147.6, 136.5, 135.4, 132.1, 131.5, 128.8,

125.2, 123.1, 118.9, 113.1, 20.3, 17.0 ppm; MS (ESI): *m/z* (%) = 265 (M^--1,100); HRMS-ESI: Calcd for $C_{16}H_{13}N_2O_2$ $(M-H)^-$ 265.0983; found: 265.0988.

2-(2-Ethylphenylamino)-8-methyl-4H-benzo[d][1,3]oxazin-4-one (**3i**): White solid; m.p. 124.1–125.2 °C; IR: ν_{max} = 3363, 2961, 1767, 1753, 1650, 1594, 1553, 1456, 1322, 1266, 1235, 1205, 1063, 1026, 756, 739, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.33–7. 25 (m, 2H), 7.18–7.13 (m, 2H), 6.59 (s, 1H), 2.70 (q, *J* = 7.6 Hz, 2H), 2.48 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.5 (C=O), 151.7, 148.2, 138.2, 136.7, 134.6, 132.0, 128.4, 125.9, 125.8, 125.7, 125.4 122.8, 112.8, 23.8, 16.8, 14.3 ppm; MS (ESI): *m/z* (%) = 281 (M^++1,100); HRMS-ESI: Calcd for $C_{17}H_{17}N_2O_2(M+H)^+$ 281.1285; found: 281.1287.

2-(3,5-Dimethylphenylamino)-8-methyl-4H-benzo[d][1,3]oxazin-4-one (**3j**): White solid; m.p. 244.2–246.3 °C; IR: ν_{max} = 3283, 3123, 2914, 1728, 1641, 1596, 1570, 1484, 1460, 1327, 1280, 1214, 1071, 1015, 844, 760, 688 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.18 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.48 (s, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.70 (s, 1H), 2.44 (s, 3H), 2.27 (s, 6H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.1 (C=O), 149.3, 147.5, 137.8, 137.3, 136.6, 132.2, 125.3, 124.0, 123.2, 116.6, 113.2, 21.2, 16.8 ppm; MS (ESI): *m/z* (%) = 279 (M^--1,100); HRMS-ESI: Calcd for $C_{17}H_{15}N_2O_2(M-H)^-$ 279.1139; found: 279.1148.

8-Methyl-2-(Naphthalen-1-ylamino)-4H-benzo[d][1,3]oxazin-4-one (**3k**): White solid; m.p. 201.8–203.0 °C; IR: ν_{max} = 3373, 3052, 1763, 1643, 1608, 1563, 1484, 1458, 1327, 1261, 1206, 1066, 1014, 784, 758, 702 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.18 (s, 1H), 8.17 (dd, 1H, J_1 = 3.6 Hz, J_2 = 6.0 Hz), 7.94 (d, *J* = 6.8 Hz, 2H), 7.78 (t, *J* = 6.8 Hz, 2H), 7.56–7.52 (m, 4H), 7.12 (t, *J* = 7.6 Hz, 1H), 2.22 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.4 (C=O), 151.6, 147.9, 136.6, 133.5, 132.6, 132.1, 127.81, 127.75, 125.8, 125.6, 125.4, 125.3, 125.2, 123.0, 122.7, 121.6, 113.1, 16.8 ppm; MS (ESI): *m/z* (%) = 301 (M^- -1, 100); HRMS-ESI: Calcd for $C_{19}H_{13}N_2O_2$ $(M-H)^-$ 301.0983; found: 301.0988.

2-(Phenylamino)-4H-benzo[d][1,3]oxazin-4-one (**3l**): White solid; m.p. 190.9–192.3 °C (lit.[9] 191–193 °C); IR: ν_{max} = 3273, 3140, 3095, 2925, 1741, 1637, 1596, 1474, 1445, 1242, 1021, 769, 706 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.31 (s, 1H), 7.98 (dd, J_1 = 1.6 Hz, J_2= 8.0 Hz, 1H), 7.80–7.74 (m, 3H), 7.37 (t, *J* = 8.0 Hz, 3H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H,) ppm; ^{13}C NMR (DMSO-d_6): δ 159.3 (C=O), 150.3, 149.2, 136.9, 136.7, 129.2, 128.8, 125.0, 124.8, 124.3, 119.9, 114.0 ppm; MS (ESI): *m/z* (%) = 239 (M^++1,100).

2-(2-Tolylamino)-4H-benzo[d][1,3]oxazin-4-one (**3m**): White solid; m.p. 154.6–156.1 °C (lit.[9] 153–155 °C); IR: ν_{max} = 3281, 3064, 1769, 1681, 1662, 1608, 1541, 1446, 1288, 1242, 1035, 752, 740 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.23 (s, 1H), 7.98–7.96 (m, 1H), 7.78–7.74 (m, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.56 (s, 1H), 7.39–7.37 (m, 1H), 7.31–7.23 (m, 2H), 6.91–6.89 (m, 1H,), 2.32 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.2 (C=O), 150.6, 149.4, 138.0, 136.8, 128.6, 128.1, 124.6, 124.2, 123.8, 120.0, 116.7, 113.9, 21.3; MS (ESI): *m/z* (%) = 253 (M^++1,100).

2-(3-Tolylamino)-4H-benzo[d][1,3]oxazin-4-one (**3n**): White solid; m.p. 176.4–178.2 °C (lit.[19] 180–182 °C); IR: ν_{max} = 3277, 3153, 3106, 1735, 1644, 1571, 1477, 1330, 1068, 765, 686 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.10 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.71–7.67 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H,), 7.43–7.41 (m, 2H), 7.30–7. 24 (m, 2H), 6.97 (d, *J* = 7.6 Hz, 1H,), 2.39 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.6, 150.2, 149.5, 139.1, 136.8, 136.7, 129.0, 128.8, 125.1, 124.7, 120.5, 117.1, 114.0, 21.6 ppm; MS (ESI): *m/z* (%) = 253(M^++1,100).

2-(4-Methoxyphenylamino)-4H-benzo[d][1,3]oxazin-4-one (**3o**): White solid; m.p. 192.9–194.4 °C (lit[9]. 193–195 °C); IR: ν_{max} = 3275, 2827, 1749, 1631, 1601, 1475, 1238, 1171, 1022, 765 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.13 (s, 1H), 7.95 (dd, *J* = 1.6 Hz, *J* = 8.0 Hz, 1H), 7.76–7.71 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28–7.23 (m, 1H), 6.96–6.94 (m, 2H), 3.75 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.2, 155.3, 150.9, 149.7, 136.7, 130.9, 128.0, 124.3, 123.8, 121.3, 114.0, 113.6, 55.2 ppm; MS (ESI): *m/z* (%) = 269 (M^++1,100).

2-(2,5-Dichlorophenylamino)-4H-benzo[d][1,3]oxazin-4-one (**3p**): White solid; m.p. 167.1–168.3 °C (lit.[19] 179–181 °C); IR: ν_{max} = 3379, 3306, 3093, 1774, 1645, 1588, 1534, 1475, 1410, 1267, 1209, 1048, 884, 808, 759 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.02 (s, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.76–7.72 (m, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.33–7.24 (m, 4H) ppm; ^{13}C NMR (DMSO-d_6): δ 158.7, 148.9, 148.2, 137.0, 134.5, 133.5, 129.8, 128.9, 125.7, 125.4, 124.1, 120.7, 120.5, 114.3 ppm; MS (ESI): *m/z* (%) = 305 (M^--1, 100), 307 (M^- +1, 65), 309 (M^- +3, 12).

2-(Naphthalen-1-ylamino)-4H-benzo[d][1,3]oxazin-4-one (**3q**): White solid; m.p. 208.5–209.7 °C; IR: ν_{max} = 3436, 3272, 3051, 1751, 1645, 1610, 1571, 1478, 1268, 759, 704, 689 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.19 (s, 1H), 8.15–8.13 (m, 1H), 8.00–7.95 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 1H,), 7.77 (d, *J* = 8.0 Hz, 1H,), 7.70–7.66 (m, 1H), 7.60–7.54 (m, 3H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ 159.2 (C=O), 150.6, 149.4, 138.0, 136.8, 128.6, 128.1, 124.6, 124.2, 123.8, 120.0, 116.7, 113.9 ppm; MS (ESI): *m/z* (%) = 289 (M^++1,100); HRMS-ESI: Calcd for $C_{18}H_{13}N_2O_2$ $(M+H)^+$ 289.0936; found 289.0938.

7-Chloro-2-(4-methoxyphenylamino)-4H-benzo[d][1,3]oxazin-4-one (**3r**): White solid; m.p. 195.0–197.5 °C; IR: ν_{max} = 3293, 3100, 1739, 1648, 1604, 1567, 1513, 1461, 1329, 1248, 1231, 1183, 1078, 1040, 933, 862, 821, 768, 723 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.24 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.32 (s, 1H), 7.23 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 6.91(d, *J* = 8.4 Hz, 2H), 3.73 (s, 3H) ppm; ^{13}C NMR(DMSO-d_6): δ = 158.3 (C=O), 155.3, 151.5, 150.8, 141.0, 130.3, 129.7, 123.6, 123.3, 121.4, 113.8, 112.3, 55.2 ppm; MS (ESI): *m/z* (%) = 301 (M^--1,100), 303 (M^-+1,33); HRMS-ESI: Calcd for $C_{15}H_{10}ClN_2O_3$ $(M-H)^-$ 301.0385; found: 301.0398.

7-Chloro-2-(4-ethoxyphenylamino)-4H-benzo[d][1,3]oxazin-4-one (**3s**): White solid; m.p. 166.6–171.4 °C; IR: ν_{max} = 3445, 3291, 2975, 1738, 1645, 1604, 1566, 1512, 1459, 1443, 1390, 1248, 1229, 1179, 1079, 1052, 934, 872, 824, 768 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.26 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.25 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.92–6.90 (m, 2H), 4.00 (q, *J* = 6.8 Hz, 2H), 1.32 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR(DMSO-d_6): δ 158.3 (C=O), 154.5, 151.5, 150.9, 141.0, 130.3, 129.7, 123.6, 123.4, 121.3, 114.3, 112.4, 63.1, 14.8 ppm; MS (ESI): *m/z* (%) = 315 (M^--1,100), 317 (M^-+1,32); HRMS-ESI: Calcd for $C_{16}H_{12}ClN_2O_3$ $(M-H)^-$ 315.0542; found: 315.0542.

7-Chloro-2-(phenylamino)-4H-benzo[d][1,3]oxazin-4-one (**3t**): White solid; m.p. 232.0–233.8 °C; IR: ν_{max} = 3448, 3285, 3147, 1736, 1659, 1592, 1567, 1499, 1459, 1334, 1264, 1232, 1199, 1080, 1057, 932, 870, 856, 770, 746, 700 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 10.42 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.37–7.33 (m, 2H), 7.29 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ 158.1 (C=O), 151.2, 150.5, 141.0, 137.4, 129.6, 128.5, 124.0, 123.5, 123.1, 119.6, 112.6 ppm; MS (ESI): *m/z* (%) = 271 (M^--1,100), 273 (M^- +1,34); HRMS-ESI: Calcd for $C_{14}H_8ClN_2O_2$ $(M-H)^-$ 271.0280; found: 271.0301.

7-Chloro-2-(2-ethylphenylamino)-4H-benzo[d][1,3]oxazin-4-one (**3u**): White solid; m.p. 158.0–160.0 °C; IR: ν_{max} = 3436.64, 3293.14, 2964.49, 1754.92, 1649.95, 1604.65, 1587.20, 1565.40, 1460.25, 1239.24, 1077.61, 878, 765.19, 740 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.81 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.41–7.39 (m, 1H), 7.30–7.28 (m, 1H), 7.25–7.20 (m, 4H), 2.64 (q, *J* = 7.2 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR(DMSO-d_6): δ 158.5 (C=O), 153.6, 151.3, 141.1, 139.3 134.0, 129.8, 128.5, 127.1, 126.5, 126.1, 123.4, 123.0, 112.0, 23.8, 14.4 ppm; MS (ESI): *m/z* (%) = 301 (M^++1,100), 303 (M^++3,33); HRMS-ESI: Calcd for $C_{16}H_{14}ClN_2O_2$ $(M+H)^+$ 301.0738; found: 301.0747.

7-Chloro-2-(3-tolylamino)-4H-benzo[d][1,3]oxazin-4-one (**3v**): White solid; m.p. 213.6–216.2 °C; IR: ν_{max} = 3437, 3289, 3060, 2920, 1734, 1662, 1607, 1596, 1574, 1495, 1463, 1443, 1334, 1250, 1227, 1061, 937, 895, 871, 777, 713 cm^{-1}; ^1H NMR(DMSO-d_6): δ 10.35 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.58–7.55 (m, 2H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.27 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.22 (t, *J* = 8.0 Hz 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 2.32 (s, 3H) ppm; ^{13}C NMR(DMSO-d_6): δ 158.1 (C=O), 151.1, 150.5, 141.0, 137.7, 137.3, 129.6, 128.3, 123.91, 123.85 123.5, 120.0, 116.7, 112.6, 21.3 ppm; MS (ESI): *m/z* (%) = 285 (M^--1,100), 287 (M^-+1,33); HRMS-ESI: Calcd for $C_{15}H_{10}ClN_2O_2$ $(M-H)^-$ 285.0436; found: 285.0438.

7-Chloro-2-(4-tolylamino)-4H-benzo[d][1,3]oxazin-4-one (**3w**): White solid; m.p. 220–221 °C; IR: ν_{max} = 3432, 3289, 3137, 2916, 1728, 1641, 1598, 1550, 1514, 1483, 1456, 1324, 1266, 1234, 1062, 1030, 817, 757, 702 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.32 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* =8.4 Hz, 2H) 7.35 (d, *J* = 2.0 Hz, 1H), 7.24 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 2.0 Hz, 1H), 7.14 (d, *J* =8.0 Hz, 2H), 2.28 (s, 3H) ppm; ^{13}C NMR(DMSO-d_6): δ 158.2 (C=O), 151.2, 150.6, 141.0, 134.8, 132.1, 129.6, 128.9, 123.8, 123.4, 119.6, 112.4, 20.5 ppm; MS (ESI): *m/z* (%) = 285 (M^--1,100), 287 (M^-+1,43); HRMS-ESI: Calcd for $C_{15}H_{10}ClN_2O_2$ $(M-H)^-$ 285.0436; found: 285.0432.

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References

1 A. Krantz, R.W. Spencer, T.F. Tam, T.J. Liak, L.J. Copp, E.M. Tomas and S.P. Rafferty, *J. Med. Chem*., 1990, **33**, 464.
2 H. Kakuta, Y. Koiso, H. Takahashi, K. Nagasawa and Y. Hashimoto, *Heterocycles*, 2001, **55**, 1433.
3 M.E. Abdel Fattah, I.I. Abdel Gawad and S.M. Mina, *Egypt. J. Chem*., 2006, **49**, 651.
4 H. Kakuta, A. Tanatani, K. Nagasawa and Y. Hashimoto, *Chem. Pharm. Bull.*, 2003, **51**, 1273.
5 S.K. Kashaw, V. Kashaw, P. Mishra, N.K. Jain and J.P. Stables, *Eur. J. Med. Chem.*, 2009, **44**, 4335.
6 G. Rotas, A. Kimbaris and G. Varvounis, *Tetrahedron*, 2011, **67**, 7805.
7 K.R. Shreder, J. Cajica, L.L. Du, A. Fraster, Y. Hu, Y. Kohno, E.C.K. Lin, S.J. Liu, E. Okerberg, L. Pham, J.Y. Wu and J.W. Kozarich, *Bioorg. Med. Chem. Lett*., 2009, **19**, 4743.
8 A. Kalusa, N. Chessum and K. Jones, *Tetrahedron. Lett*., 2008, **49**, 5840.
9 J. Garin, E. Melendez, F.L. Merchan, T. Tejero and E. Villarroya, *Synthesis*, 1983, 406.
10 P. Molina, E. Aller, M. Ecija and A. Lorenzo, *Synthesis*, 1996, 690.
11 J.G. Fernández-Bolaños, Ó. López, V. Ulgar, I. Maya and J. Fuentes, *Tetrahedron Lett.*, 2004, **45**, 4081.
12 G.L. Sommen, A. Linden and H. Heimgartner, *Eur. J. Org. Chem.*, 2005, 3128.
13 D.R. Garud, M. Makimura, H. Ando, H. Ishihara and M. Koketsu, *Tetrahedron Lett.*, 2007, **48**, 7764.
14 D.R. Garud and M. Koketsu, *Org. Lett.*, 2008, **10**, 3319.
15 D.R. Garud, Y. Toyoda and M. Koketsu, *Tetrahedron Lett.*, 2009, **50**, 3035.
16 G.L. Sommen, A. Linden and H. Heimgartner, *Tetrahedron*, 2006, **62**, 3344.
17 D.R. Garud, M. Koketsu, *Org. Lett.*, 2008, **10**, 3319.
18 Y.Y. Xie, J.L. Liu, P. Yang, X.J. Shi and J.J. Li, *Tetrahedron*, 2011, **67**, 5369.
19 E.P. Papadopoulos and C.D. Torres, *J. Heterocycl. Chem.*,1982, **19**, 269.
20 S.H. Jung, J.H. Ahn, S.K. Park and J.K. Choi, *Bull. Korean Chem. Soc.*, 2002, **23**, 149.
21 W.K. Su and X.R. Liang, *J. Indian Chem. Soc.*, 2003, **80**, 645.