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Research Article

A FACILE 1,2,4-OXADIAZOLE DERIVATIVES SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION

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ABSTRACT

The reaction of benzamidoxime with chloroacetyl chloride in the presence of organic base proceed smoothly under refluxing condition in 2-dichloro ethane to give the corresponding substituted 3-(4-bromo-2-fluorophenyl)-5-(chloromethyl)-1,2,4-oxadiazole. It reacts with different substituted phenol generate a series of novel 1,2,4-oxadiazole compounds. All synthesized compounds were characterized by using elemental analysis, Mass, IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Also compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains.

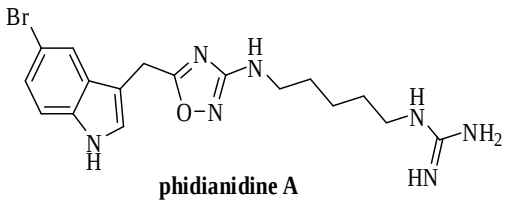
Keywords: N-ethyl-N,N-diisopropylamine, N'-hydroxybenzamidine.

INTRODUCTION

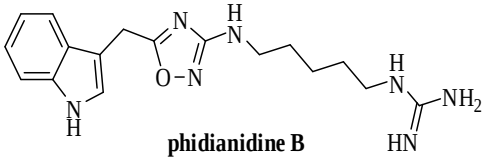
The five-membered heterocyclic 1,2,4-oxadiazole moiety is of synthetic and pharmacological interest.It also forms an importantconstituent of biologically active compounds includingnatural products[1]. Sawyer et al. have described such compoundsas bioisosteres for amides and esters[2], with the 1,2,4-oxadiazoles showing higher hydrolytic and metabolic stability.

The 3-substituted indole alkaloids, phidianidines Aand B (Figure 1), have been isolated by Carbone et al. from theaeolidopisthobranch*Phidianamilitaris*[3]

Furthermore, substituted 1,2,4-oxadiazoles have been described as antirhinovirals[4], benzodiazepine receptor partial agonists[5], anti-inflammatory[6] muscarinic agonists[7] serotoninergic (5-HT3) antagonists[8] and growth hormone secretagogues[9].



phidianidine A



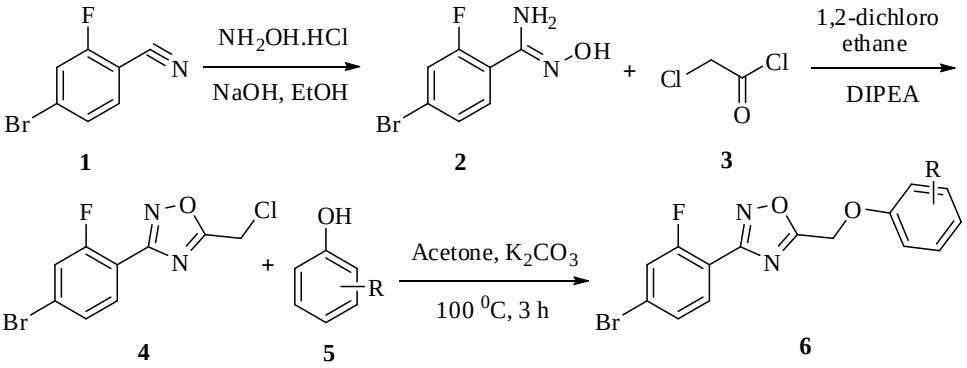
phidianidine B

Fig. 1: Natural products having 1,2,4-oxadiazole core

Reaction scheme

The synthesis of new 1,2,3-oxadiazole derivatives **6a-k** were performed by the nucleophilic substitution of chlorine atom in 3-(4-bromo-2-fluorophenyl)-5-(chloromethyl)-1,2,4-oxadiazole**(4)** by various substituted phenol **(5a-k)**(scheme - 1). final compounds were purified by column chromatography using Hexane/Ethylacetate mixture. 3-(4-bromo-2-fluorophenyl)-5-(chloromethyl)-1,2,4-oxadiazole**(4)** were synthesized by the reaction of 4-bromo-2-fluorobenzonitrile **(1)** with hydroxylamine hydrochloride in ethanol

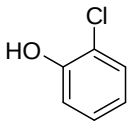
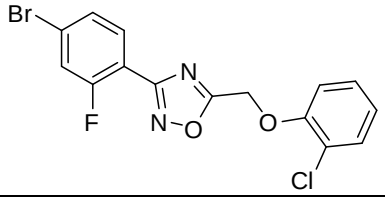
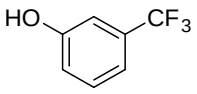
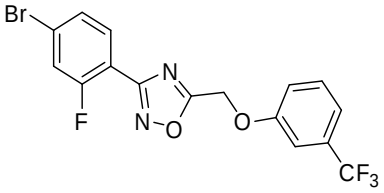
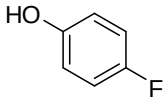
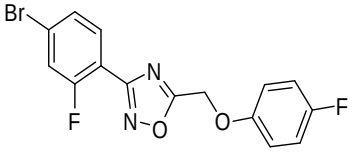
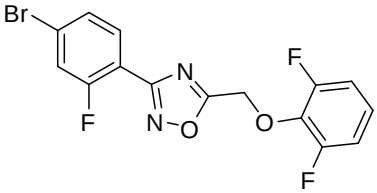
followed by the cyclization with chloroacetyl chloride **(3)**in 1,2-dichloro ethane using N-ethyl-N,N-diisopropylamine (DIPEA) as a base. 4-bromo-2-fluorobenzonitrile **(1)**react with hydroxylamine hydrochloride in ethanol using NaOH base to yield 4-bromo-2-fluoro-N'-hydroxybenzamidine **(2).**

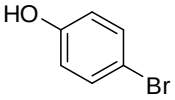
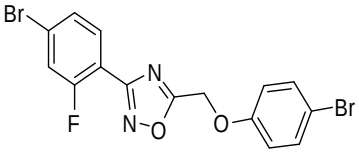
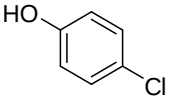
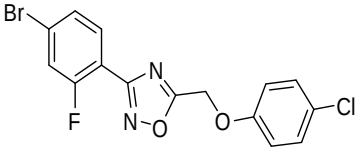
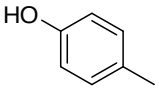
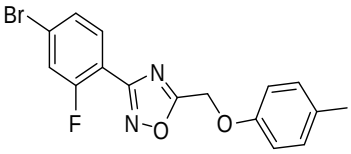
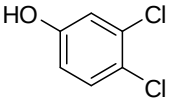
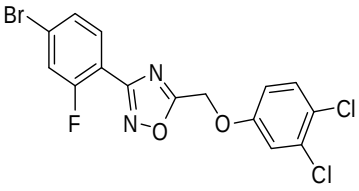
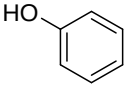
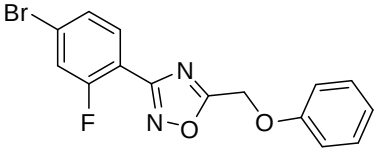
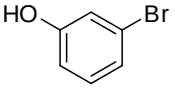
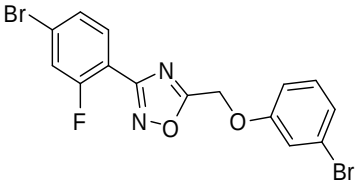
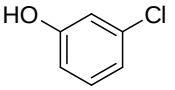
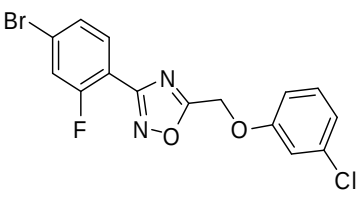


Scheme. 1: Reagents and condition (1) EtOH,$NH_2OH.HCl$, NaOH, reflux (2) 1,2-dichloroethane, DIPEA (3) Acetone, K_2CO_3, 100 ^oC, 3h.

RESULTS AND DISCUSSION

Table 1: phenol coupled 1,2,4-oxadiazole derivatives

Entry	Phenol	Product	Time (h)	Yield[a] (%)	Mp (°C)
1			2	72	185-187
2			3	69	216-219
3			1	78	211
4			2	72	232-234

5			3	74	191-193
6			2	76	228
7			2	78	237-239
8			3	73	243-246
9			2	80	179-181
10			3	73	183-186
11			3	72	224-227

[a]yield after purification

CONCLUSIONS

In summary, we have reported a general and efficient protocol for the preparation of various 1,2,4-oxadiazole derivativesresulted from substituted benzonitrile. Reactions occur using the environmentally safe medium, products are rapidly formed in good yields, no complex operation or handling is required, and use of toxic organic solvents is avoided. The investigation of antibacterial and antifungal screening revealed that some of these agents possesses moderate to significant activity.

Experimental

Reactions were monitored by TLC using silica-gel coated plates and ethyl acetate/hexanes solutions as the mobile phase, spots were located by iodine and UV. Melting points are

uncorrected. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions are reported as wave numbers (cm-1). 1H NMR and 13C NMR spectra were obtained on a FT-NMR Bruker Ultra ShieldTM (400 MHz) instrument asDMSO-d_6 solutions and the chemical shifts are expressed as units with Me4Si as the internal standard.Mass spectra were recorded on direct inlet probe on a **GCMS-QP 2010** mass spectrometer (Shimadzu). Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument.All other chemicals were purchased from commercial sources and were used after being freshly purified by standard procedures.

Typical procedure

To a stirred suspension of 3-(4-bromo-2-fluorophenyl)-5-(chloromethyl)-1,2,4-oxadiazole (290mg, 1 mmol) in 10 mL of acetone was added 2-chlorophenol (180mg, 1 mmol) and K_2CO_3 (166mg, 1.2 mmol). Then it was stirred for 2-3 hours under reflux. The resulting solution was directly concentrated in vacuo to remove acetone. The residue was diluted with water and extract with ethyl acetate. The organic phase was separated and subsequently washed with 10% sodium hydroxide solution and brine. Organic phase was dried over sodium sulphate and filtered. The filtrate was evaporated under reduce pressure to obtained crude[10]. it was purified by column chromatography using EtOAc/hexanes mixture. Compound **6a** was obtained in 72% yield (275mg).The product was identified based on its physical and spectral characteristics.

5-((2-chlorophenoxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole(6a)

cream solid,Yield: 72%; mp 185-187 ^oC; MS (m/z): calculated for $C_{15}H_9BrClFN_2O_2$(M^++H):382; C, 46.97; H, 2.36; Br, 20.83; Cl, 9.24; F, 4.95; N, 7.30; O, 8.34; Found: C, 46.78; H, 2.54; Br, 20.73; Cl, 9.46; F, 4.82; N, 7.26; O, 8.41.IR (cm^{-1}): 1606 (C=C), 1502 (C=C), 1490 (C=C), 1352 (C-H), 1210 (C-N), 1102 (C-O), 1002 (C-F), 823, 681 (C-Br).^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.96 (t, 1H), 7.86 (d, 1H), 7.66 (d, 1H), 7.20-7.10 (m, 4H), 5.61 (s, 2H) ppm; ^{13}C NMR (400 MHz, DMSO-d_6) δ : 175, 163, 160, 158, 156, 153, 131, 128, 125, 120, 116, 113, 61 ppm.

5-((3-(trifluoromethyl)phenoxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxa-diazole(6b)

cream solid,Yield: 69%; mp 216-219 ^oC; MS (m/z): calculated for $C_{16}H_9BrF_4N_2O_2$(M^++H):416; C, 46.07; H, 2.17; Br, 19.15; F, 18.22; N, 6.72; O, 7.67; Found: C, 46.23; H, 2.38; Br, 19.03; F, 18.15; N, 6.86; O, 7.35.IR (cm^{-1}): 2918 (C-H), 2834 (C-H), 1617 (C=C), 1582 (C=C), 1473 (C=C), 1325 (C-H), 1264 (C-N), 1227 (C-N),1138 (C-O), 1021 (C-F), 887, 768, 657.^{1}H NMR (400 MHz, DMSO-d_6) δ :7.93 (t, 1H), 7.86 (d, 1H), 7.74 (s, 1H), 7.67 (d,1H), 7.63 (d, 1H), 7.49 (d, 1H) , 7.23 (t, 1H), 5.64 (s, 2H) ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ : 176, 164, 162, 160, 154,152, 148, 130, 129,126, 120, 118, 111,62 ppm.

5-((4-fluorophenoxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole(6c)

white solid,Yield: 78%; mp 211 ^oC; MS (m/z): calculated for $C_{15}H_9BrF_2N_2O_2$(M^++H):366; C, 49.07; H, 2.47; Br, 21.76; F, 10.35; N, 7.63; O, 8.72; Found: C, 49.31; H, 2.25; Br, 21.52; F, 10.57; N, 7.61; O, 8.74.IR (cm^{-1}): 3107 (C-H), 2920 (C-H), 1554 (C=C), 1521 (C=C), 1492 (C=C), 1396 (C-H), 1303 (C-H), 1242 (C-N), 1138 (C-O), 1012 (C-F), 827, 779, 680 (C-Br). ^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.96 (t, 1H), 7.87 (dd, 1H), 7.66 (dd, 1.6Hz, 1H), 7.50 (dd, 1H), 7.37-7.30 (m, 2H), 7.08-7.04 (m, 1H), 5.75 (s, 2H)ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ : 176, 163, 161, 160,158, 153, 129, 125, 122, 120, 119, 117, 61 ppm.

5-((2,6-difluorophenoxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole(6d)

off white solid,Yield: 72%; mp 232-234 ^oC; MS (m/z): calculated for $C_{15}H_8BrF_3N_2O_2$(M^++H): 384; C, 46.78; H, 2.09; Br, 20.75; F, 14.80; N, 7.27; O, 8.31; Found: C, 46.42; H, 2.35; Br, 20.89; F, 14.63; N, 7.54; O, 8.17.IR (cm^{-1}): 3070 (C-H), 2987 (C-H), 2802 (C-H), 1599 (C=C), 1531 (C=C), 1492 (C=C), 1342 (C-H), 1244 (C-N), 1226 (C-N), 1138 (C-O), 1012 (C-F), 833, 661 (C-Br). ^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.95 (t, 1H), 7.85 (d, 1H), 7.64 (d, 1H), 7.16-7.08 (m, 3H), 5.56 (s, 2H) ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ : 175, 163, 161, 159, 158, 154, 138, 128, 126,124, 120, 115, 114, 62 ppm.

5-((4-bromophenoxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole(6e)

cream solid, Yield: 74%; mp 191-193 ^oC; MS (m/z): calculated for $C_{15}H_9Br_2FN_2O_2$(M^++H):426; C, 42.09; H, 2.12; Br, 37.33; F, 4.44; N, 6.54; O, 7.48; Found: C, 42.16; H, 2.19; Br, 37.42; F, 4.11; N, 6.49; O, 7.63.IR (cm^{-1}): 3063 (C-H), 2974 (C-H), 2843 (C-H), 1607 (C=C), 1492 (C=C), 1434 (C=C), 1381 (C-H), 1329 (C-H), 1254 (C-N), 1145 (C-O), 1014 (C-F), 857, 667 (C-Br).^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.94 (t, 1H), 7.89-7.74 (m, 3H), 7.68 (d, 1H), 7.61 (dd, 2H), 5.75 (s, 2H) ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ : 176, 164,

161, 160, 154, 147, 146,128, 125, 120, 119, 118, 114, 61 ppm.

5-((*4-chlorophenoxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole(6f)*

off white solid, Yield: 76%; mp 228 °C; MS (m/z): calculated for $C_{15}H_9BrClFN_2O_2$(M^++H):382; C, 46.97; H, 2.36; Br, 20.83; Cl, 9.24; F, 4.95; N, 7.30; O, 8.34; Found: C, 46.68; H, 2.56; Br, 20.71; Cl, 9.53; F, 4.74; N, 7.17; O, 8.61.IR (cm^{-1}): 3043 (C-H), 2908 (C-H), 2863 (C-H), 1564 (C=C), 1492 (C=C), 1372 (C-H), 1309 (C-H), 1281 (C-N), 1157 (C-O), 1104 (C-O), 831,651 (C-Br). ^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.92 (t, J = 8.4, 7.6 Hz, 1H), 7.85 (d, 1H), 7.68 (d, 1H), 7.56 (dd, 1H), 7.38(dd, 1H), 7.08-7.04 (m, 1H), 5.71 (s, 2H) ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ : 175, 164, 160, 159,153, 133, 132, 129,127, 125, 120, 119,61 ppm.

5-((*p-tolyloxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole(6g)*

off white solid, Yield: 78%; mp 237-239 °C; MS (m/z): calculated for $C_{16}H_{12}BrFN_2O_2$(M^++H):362; C, 52.91; H, 3.33; Br, 22.00; F, 5.23; N, 7.71; O, 8.81; Found: C, 52.71; H, 3.48; Br, 22.17; F, 5.34; N, 7.46; O, 8.84.IR (cm^{-1}): 3058 (C-H), 2924 (C-H), 2879 (C-H) 2813 (C-H), 1583 (C=C), 1496 (C=C), 1452 (C=C), 1375 (C-H), 1316 (C-H), 1263 (C-N), 1174 (C-O), 1017 (C-F), 819, 754, 673 (C-Br).^{1}H NMR (400 MHz, DMSO-d_6) δ :7.89 (t, 1H), 7.80 (d, 1H), 7.68 (d, 1H), 7.56 (dd, 2H), 7.08 (dd, 2H), 2.63 (s, 1H), 5.62 (s, 2H) ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ : 176, 163, 160, 158,154, 138, 136, 135, 129, 126, 120, 116, 115, 61, 19 ppm.

5-((*3,4-dichlorophenoxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole(6h)*

white solid, Yield: 73%; mp 243-246 °C; MS (m/z): calculated for $C_{15}H_8BrCl_2FN_2O_2$(M^++H):416; C, 43.10; H, 1.93; Br, 19.11; Cl, 16.96; F, 4.54; N, 6.70; O, 7.65; Found: C, 43.29; H, 1.76; Br, 19.28; Cl, 16.83; F, 4.73; N, 6.57; O, 7.54.IR (cm^{-1}): 3070 (C-H), 2927 (C-H), 2857 (C-H), 1590 (C=C), 1451 (C=C), 1374 (C-H), 1335 (C-H), 1231 (C-N), 1134 (C-O), 1109 (C-O), 1004 (C-F), 834, 772 (C-Cl), 639 (C-Br). ^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.95 (t, 1H), 7.87 (d, 1H), 7.70 (d, 1H), 7.63 (d, 1H), 7.54 (s, 1H), 7.08 (d, 1H), 5.67 (s, 2H) ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ : 176, 164, 162, 161, 154, 148, 145, 128, 127, 125, 119, 118, 61 ppm.

3-(4-bromo-2-fluorophenyl)-5-((phenoxy)methyl)-1,2,4-oxadiazole(6i)

cream solid, Yield: 80%; mp 179-181 °C; MS (m/z): calculated for $C_{15}H_{10}BrFN_2O_2$(M^++H):348; C, 51.60; H, 2.89; Br, 22.88; F, 5.44; N, 8.02; O, 9.16; Found: C, 51.42; H, 2.73; Br, 22.96; F, 5.63; N, 8.14; O, 9.12.IR (cm^{-1}): 3085 (C-H), 2981 (C-H), 2847 (C-H), 1594 (C=C), 1488 (C=C), 1306 (C-H), 1232 (C-N), 1135 (C-O), 1017 (C-F), 745, 694, 643 (C-Br). ^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.92 (t, 1H), 7.84 (d, 1H), 7.65 (d, 1H), 7.32-7.29 (m, 2H), 6.98-7.03 (m, 3H), 5.72 (s, 2H) ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ : 175, 164, 161, 156, 154, 132, 131, 128, 126, 121, 120, 115, 61 ppm.

5-((*3-bromophenoxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole(6j)*

white solid, Yield: 73%; mp 183-186 °C; MS (m/z): calculated for $C_{15}H_9Br_2FN_2O_2$(M^++H):426; C, 42.09; H, 2.12; Br, 37.33; F, 4.44; N, 6.54; O, 7.48; Found: C, 42.21; H, 2.37; Br, 37.26; F, 4.38; N, 6.15; O, 7.63.IR (cm^{-1}): 3062 (C-H), 2917 (C-H), 2864 (C-H), 1608 (C=C), 1527 (C=C), 1468 (C=C), 1375 (C-H), 1317 (C-H), 1259 (C-N), 1164 (C-O), 873, 784, 678 (C-Br). ^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.93 (t, J = 8 Hz, 1H), 7.86 (d, 1H), 7.69 (s, 1H), 7.67 (d, 1H), 7.57 (d, 1H), 7.41 (d, 1H) , 7.11 (t, 1H), 5.59 (s, 2H) ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ: 176, 165, 164, 163, 154, 138, 129, 126, 125, 123, 120, 119, 114, 61 ppm.

5-((*3-chlorophenoxy)methyl)-3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole(6k)*

off white solid.Yield: 72%; mp 224-227 °C; MS (m/z): calculated for $C_{15}H_9BrClFN_2O_2$(M^++H):382; C, 46.97; H, 2.36; Br, 20.83; Cl, 9.24; F, 4.95; N, 7.30; O, 8.34; Found: C, 46.82; H, 2.46; Br, 20.69; Cl, 9.48; F, 4.79; N, 7.30; O, 8.46.IR (cm^{-1}): 3037 (C-H), 2905 (C-H), 2812 (C-H), 1612 (C=C), 1494 (C=C), 1443 (C=C), 1381 (C-H), 1312 (C-H), 1223 (C-N), 1105 (C-O), 1005 (C-F), 834, 762 (C-Cl), 682 (C-Br).^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.91 (t, 1H), 7.84 (d, 1H), 7.71 (s, 1H), 7.66 (d, 1H), 7.61 (d, 1H) , 7.17 (t, 1H), 5.64 (s, 2H) ppm.^{13}C NMR (400 MHz, DMSO-d_6) δ : 176, 164, 163, 162, 153, 137, 128, 126, 124, 121, 119, 117, 113, 61 ppm.

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REFERENCES

1. Jochims JC, Katritzky AR, Rees CW and Scriven EV. Eds. ComprehensiveHeterocyclic Chemistry II. 1996;4:179–228.
2. Vu CB, Corpuz EG, Merry TJ, Pradeepan SG, Bartlett C, Bohacek RS, Botfield MC, Eyermann CJ, Lynch BA, MacNeil IA, Ram MK, van Schravendijk MR, Violette S and Sawyer TK. J Med Chem. 1999;42:4088–4098.

3. Carbone MY, Irace C, Mollo E, Castelluccio F, Di Pascale A, Cimino G, Santamaria R, Guo Y W and Gavagnin M. Org Lett. 2011;13:2516–2519.
4. Diana GD, Volkots DL, Nitz TJ, Bailey TR, Long MA, Vescio N, Aldous S, Pevear DC and Dutko FJ. J Med Chem. 1994;37:2421–2436.
5. Watjen F, Baker R, Engelstoff M, Herbert R, MacLeod A, Knight A, Merchant K, Moseley J, Saunders J, Swain CJ, Wong E and Springer JP. J Med Chem. 1989;32:2282–2291.
6. Bezerra NM, De Oliveira SP, Srivastava RM and Da Silva JR. Farmaco. 2005;60:955–960.
7. Orlek BS, Blaney FE, Brown F, Clark MS, Hadley MS, Hatcher J, Riley GJ, Rosenberg HE, Wadsworth HJ and Wyman PJ. J Me. Chem. 1991;34:2726–2735.
8. Swain CJ, Baker R, Kneen C, Moseley J, Saunders J, Seward EM, Stevenson G, Beer M, Stanton J and Watling KJ. Med Chem. 1991;34:140–151.
9. Ankersen M, Peschke B, Hansen BS and Hansen TK. Bioorg Med Chem Lett. 1997;7:1293–1298.
10. Patent: Oslo University Hospital Hf, Holsworth Dan, Waaler Jo, Machon Ondrej, Krauss Stefan and Golding Louise. WO2010/139966; 2010; (A1) English.