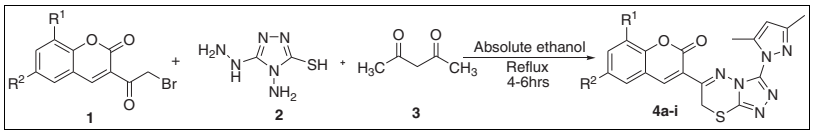
Sreenu Pavurala and Rajeswar Rao Vedula*

Department of Chemistry, National Institute of Technology, Warangal 506 004, Andhra Pradesh, India
*E-mail: vrajesw@yahoo.com

Additional Supporting Information may be found in the online version of this article.
Received December 21, 2012
DOI 10.1002/jhet.2027
Published online 20 May 2014 in Wiley Online Library (wileyonlinelibrary.com).



One-pot synthesis of 3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-2*H*-chromen-2-ones was achieved via the multicomponent reaction of purpald, acetyl acetone, and different derivatives of 3-(2-bromo-acetyl)-2*H*-chromen-2-one in absolute ethanol. All the synthesized compounds were characterized by analytical and spectral data.

J. Heterocyclic Chem., **52**, 306 (2015).

INTRODUCTION

Triazoles and their derivatives show a broad range of biological activities [1], such as analgesic, antibacterial [2], anthelmintic [3], antiviral [4], antifungal [4], anticancer properties [5], and plant growth regulating [6]. Molecules with 7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine systems [7] were also reported to show a broad spectrum of pharmacological properties such as antifungal [8], antibacterial [9], antiviral [10], antihelmentic [11], antitumor [12], anti-inflammatory [13], antitubercular [14], diuretics [15], anticancer [16], antimicrobial [17], and hypoglycemic [18].

Pyrazoles and their derivatives are important compounds for various applications. They are known for their antimicrobial [19], antiviral [20], antibacterial [21], anti-inflammatory [22], antitumor [23,24], anticonvulsant [25], and cytotoxic activities [26].

Most of coumarins exhibit high levels of biological [27] and pharmacological activities including inhibition of platelet aggregation [28], anticancer [29], inhibition of steroid 5-reductase [30], antibacterial [31], anticoagulant [32], and treatment for lymphedema [33].

Recently, multicomponent reactions became widely used in organic synthesis because of several advantages such as high efficiency, atom economy, convergence, exploratory power, higher yields, cleaner reactions, and simple procedures, leading to the straightforward synthesis of new structures [34].

RESULTS AND DISCUSSION

By considering the importance of the newly synthesized heterocyclic moieties and in continuation of our earlier work on the development of useful new synthetic methodologies, we developed an efficient method for the synthesis of the title compounds (Scheme 1).

An equimolar mixture of various 3-(2-bromo-acetyl)-chromen-2-ones, purpald, and acetyl acetone refluxed in absolute ethanol for 4 h gave the title compounds. The formation of the product can be explained by the intermolecular cyclization of purpald with 3-(2-bromo-acetyl)-chromen-2-one and acetyl acetone (Scheme 2).

The structures of the aforementioned compounds were confirmed by spectral data. For example, in the IR spectrum, it gave a peak at 1704 cm^{-1} due to lactone CO. The ^1H NMR spectrum of compound **4a** gave two singlets of two CH_3 groups at δ 2.17, 2.29, the $–CH_2$ protons of thiadiazine appeared at δ 4.37, the pyrazole proton appeared at δ 6.18, and the C-4 of coumarin appeared at δ 8.45. The ^{13}C NMR spectrum of **4a** shows peaks at δ 11.6, 13.6 for two methyl carbons of pyrazole, the $–CH_2$ carbon of thiadiazine ring appeared at δ 24.4, and lactone carbon appeared at δ 159.1, respectively. The compound **4a** in the mass spectrum gave a peak at 379 cm^{-1} due to $[M+H]^+$ (Table 1).

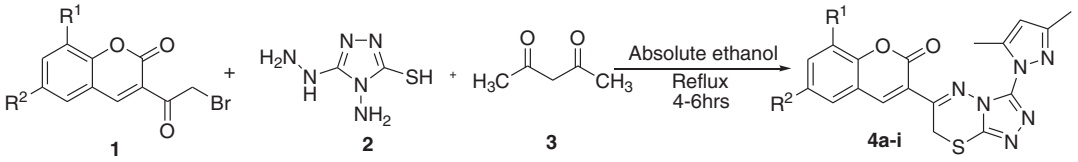
CONCLUSION

In conclusion, we have synthesized a new series of 3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazin-6-yl)-2*H*-chromen-2-ones via multicomponent reaction. The method has several advantages such as less reaction time, good yields, and easy workup.

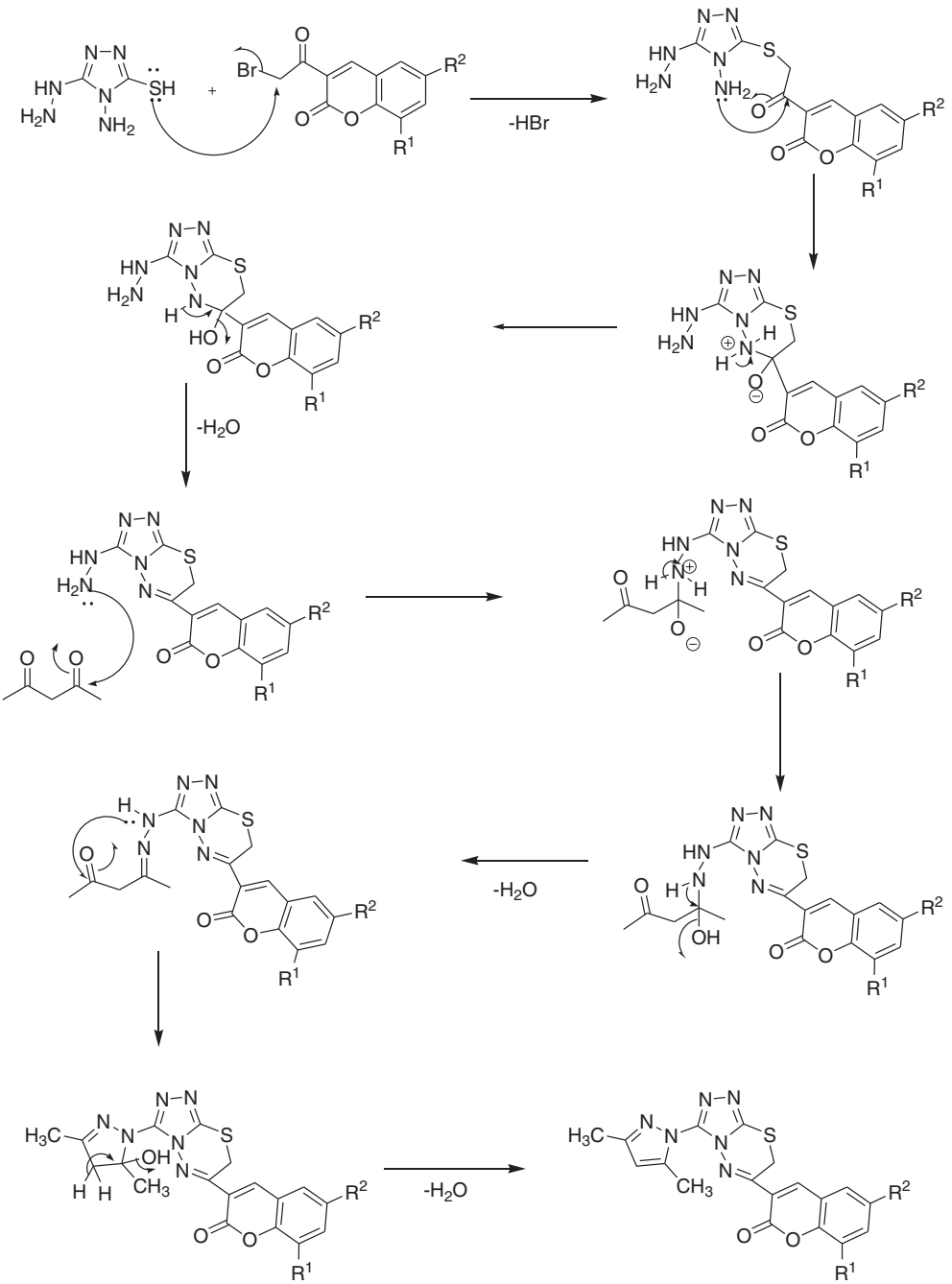
EXPERIMENTAL

All the reagents and solvents were purchased from commercial sources and were used without further purification unless otherwise stated. 3-(2-Bromo-acetyl)coumarins [35] were prepared by the literature procedure. Melting points were determined in open capillaries with a "Stuart" melting point apparatus, Mumbai, India, and were uncorrected. CHNS analysis was carried out by Carlo Erba EA 1108 automatic elemental analyzer. The purity of

Scheme 1



Scheme 2. Plausible mechanism.



the compounds was checked by TLC plates (E. Merck Mumbai, India). IR spectra were recorded on a Thermo Nicolet Nexus 670 instrument (KBr pellets). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ parts per million using TMS as the standard. ESI-MS were determined on a PerkinElmer spectrometer (SCIEX API-2000, ESI) at 12.5 eV.

Table 1

Synthesis of 3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-2*H*-chromen-2-ones.

			Absolute ethanol	
Product **4**	R_1	R_2	Time (h)	Yield (%)
4a	H	H	4	90
4b	OCH_3	H	4	85
4c	H	Cl	4	84
4d	H	Br	4	82
4e	$N(C_2H_5)_2$	H	4	85
4f	5,6-Benzo		5	80
4g	Br	Br	6	83
4h	Cl	Cl	6	82
4i	NO_2	H	4	80

General procedure for the synthesis of compounds (4a–i). 3-(2-Bromo-acetyl)-2*H*-chromen-2-one (1 mmol), purpald (1 mmol), and acetyl acetone (1 mmol) were taken in a round-bottom flask and treated with 10 mL of absolute ethanol and refluxed for 4 h. After completion of reaction, the reaction mixture was cooled, and the solid separated was filtered. The compounds were recrystallized from a mixture of chloroform and methanol.

3-[3-(3,5-Dimethyl-pyrazol-1-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-6-yl]chromen-2-one (4a). Color: yellow solid; Yield 90%; mp 249–250°C; IR (KBr, υ max/cm^{-1}): 1707 (lactone CO), 1586 (CN). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3 of pyrazole), 2.29 (s, 3H, CH_3 of pyrazole),, 4.37 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 7.40–7.44 (m, 1H, ArH), 7.50 (d, 1H, J = 8.4 Hz, ArH), 7.71–7.76 (m, 1H, ArH),7.89 (t, 1H, J = 7.6 Hz, ArH), 8.45 (s, 1H, C-4 of coumarin). ^{13}C NMR ($CDCl_3$, δ ppm): 11.6, 13.6, 24.4, 108.2, 116.0, 116.8, 118.3, 121.7, 125.2, 129.5, 134.1, 142.9, 143.5, 145.5, 147.0, 152.2, 152.8, 154.6, 159.1. ESI-MS 379 $[M+H]^+$; *Anal*. Calcd for: $C_{18}H_{14}N_6O_2S$: C, 57.13; H, 3.73; N, 22.21; S, 8.47. Found: C, 57.17; H, 3.77; N, 22.25; S, 8.51%.

8-Methoxy-3-(3-(3,5-dimethyl-1H-pyrazol-1-yl)-7H-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazin-6-yl)-2H-chromen-2-one (4b). Color: yellow solid; Yield 85%; mp 223–225°C; IR (KBr, υ max/cm^{-1}): 1704 (lactone CO), 1577 (CN), 1282 (C–OCH_3, ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3 of pyrazole), 2.28 (s, 3H, CH_3 of pyrazole), 3.93 (s, 3H, CH_3 of methoxy), 4.36 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 7.33–7.43 (m, 3H, ArH), 8.41 (s, 1H, C-4 of Coumarin).^{13}C NMR (DMSO-d_6, δ ppm): 10.8, 13.2, 24.3, 56.2, 107.6, 116.0, 118.7, 120.9, 122.6, 125.0, 143.0, 143.2, 144.8, 146.3, 151.0, 154.7, 158.2. ESI-MS 409 $[M+H]^+$; *Anal*. Calcd for $C_{19}H_{16}N_6O_3S$: C, 55.87; H, 3.95; N, 20.58; S, 7.85. Found: C, 55.83; H, 3.91; N, 20.62; S, 7.89%.

6-Chloro-3-(3-(3,5-dimethyl-1H-pyrazol-1-yl)-7H-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazin-6-yl)-2H-chromen-2-one (4c). Color: yellow solid; Yield 84%; mp 237–239°C; IR (KBr, υ max/cm^{-1}): 1708 (lactone CO), 1561(CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3 of pyrazole), 2.29 (s, 3H, CH_3 of pyrazole), 4.36 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 7.54 (d, 1H, J = 8.8 Hz, ArH), 7.75–7.78 (m, 1H, ArH), 8.04 (d, 1H, J = 2.4 Hz, ArH), 8.38 (s, 1H, C-4 of coumarin). ^{13}C NMR ($CDCl_3$, δ ppm): 11.7, 13.6, 24.3, 108.2, 118.3, 119.2, 122.9, 128.5, 130.6, 133.9, 142.8, 143.5, 144.0, 147.1, 152.3, 152.9, 158.5. ESI-MS 413 $[M+H]^+$; *Anal*. Calcd for $C_{18}H_{13}ClN_6O_2S$: C, 52.37; H, 3.17; N, 20.36; S, 7.77. Found: C, 52.34; H, 3.19; N, 20.21; S, 7.72%.

6-Bromo-3-(3-(3,5-dimethyl-1H-pyrazol-1-yl)-7H-[1,2,4]triazolo [3,4-b]{[1,3,4]thiadiazin-6-yl)-2H-chromen-2-one (4d). Color: yellow solid; Yield 82%; mp 249–250°C; IR (KBr, υ max/cm^{-1}): 1727 (lactone CO), 1578 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3 of pyrazole), 2.29 (s, 3H, CH_3 of pyrazole), 4.36 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 7.48 (d, 1H, J = 8.8 Hz, ArH), 7.86–7.89 (m, 1H, ArH), 8.17 (d, 1H, J = 2.0 Hz, ArH), 8.37 (s, 1H, C-4 of coumarin). ^{13}C NMR ($CDCl_{3+}$ DMSO-d_6, δ ppm): 11.5, 13.5, 24.2, 108.1, 117.7, 118.4, 119.6, 122.8, 131.4, 136.6, 142.7, 143.3, 143.8, 147.0, 152.2, 153.2, 158.3. *Anal*. Calcd for $C_{18}H_{13}BrN_6O_2S$: C, 47.28; H, 2.87; N, 18.38; S, 7.01. Found: C, 47.24; H, 2.84; N, 18.34; S, 7.10%.

6-(Diethylamino)-3-(3-(3,5-dimethyl-1H-pyrazol-1-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-2H-chromen-2-one (4e). Color: yellow solid; Yield 85%; mp 244–246°C; IR (KBr, υ max/cm^{-1}): 1708 (lactone CO), 1579 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13(t, 6H, CH_3 of di ethyl amine), 2.18 (t, 3H, CH_3 of pyrazole), 2.27 (s, 3H, CH_3 of pyrazole), 3.48 (q, 4H, CH_2 of di ethyl amine), 4.33 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 6.61 (d, 1H, J = 2 Hz, ArH), 6.77–6.79 (m, 1H, ArH), 7.60 (d, 1H, J = 8.8 Hz, ArH), 8.22 (s, 1H, C-4 of coumarin). ^{13}C NMR (DMSO-d_6, δ ppm): 11.0, 12.4, 13.3, 24.4, 44.4, 96.2, 107.5, 107.7, 110.1, 112.5, 131.5, 143.1, 143.4, 145.2, 146.3, 151.0, 152.5, 155.6, 157.5. ESI-MS 450 $[M+H]^+$; *Anal*. Calcd for $C_{22}H_{23}N_7O_2S$: C, 58.78; H, 5.16; N, 21.81; S, 7.13. Found: C, 47.32; H, 2.91; N, 18.32; S, 7.00%.

2-[3-(3,5-Dimethyl-pyrazol-1-yl)-7H-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazin-6-yl]benzo[f] chromen-3-one (4f). Color: yellow solid; Yield 80%; mp 255–257°C; IR (KBr, υ max/cm^{-1}): 1707 (lactone CO), 1578 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18 (s, 3H, CH_3 of pyrazole), 2.34 (s, 3H, CH_3 of pyrazole), 4.43 (s, 2H, thiadiazine), 6.19 (s, 1H, pyrazole), 7.66 (t, 2H, J = 7.4 Hz, ArH), 7.77 (t, 1H, J = 7.4 Hz, ArH), 8.11 (d, 1H, J = 7.6 Hz, ArH), 8.33 (d, 1H, J = 8.8 Hz, ArH), 8.56 (d, 1H, J = 8 Hz, ArH) 9.22 (s, 1H, C-4 of coumarin). ESI-MS 429 $[M+H]^+$; *Anal*. Calcd for $C_{22}H_{16}N_6O_2S$: C, 61.67; H, 3.76; N, 19.61; S, 7.48. Found: C, 61.70; H, 3.79; N, 19.65; S, 7.51%.

6,8-Dibromo-3-[3-(3,5-dimethyl-pyrazol-1-yl)-7H-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazin-6-yl]-chromen-2-one (4g). Color: yellow solid; Yield 83%; mp 200–201°C; IR (KBr, υ max/cm^{-1}): 1747 (lactone CO), 1599 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3 of pyrazole), 2.28 (s, 3H, CH_3 of pyrazole), 4.35 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 7.87 (d, 1H, J = 2.4 Hz, ArH), 7.89 (d, 1H, J = 2.4 Hz ArH), 8.49 (s, 1H, C-4 of coumarin). *Anal*. Calcd for $C_{18}H_{12}Br_2N_6O_2S$: C, 40.32; H, 2.26; N, 15.67; S, 5.98. Found: C, 40.35; H, 2.30; N, 15.70; S, 5.90%.

6,8-Dichloro-3-[3-(3,5-dimethyl-pyrazol-1-yl)-7H-[1,2,4]triazolo [3,4- b][1,3,4] thiadiazin-6-yl]-chromen-2-one (4h). Color: yellow solid; Yield 82%; mp 242–244°C; IR (KBr, υ max/cm^{-1}): 1728 (lactone CO), 1587 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3 of pyrazole), 2.28 (s, 3H, CH_3 of pyrazole), 4.36 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 7.75 (d, 1H, J = 2.8 Hz, ArH), 7.77 (d, 1H, J = 2.4 Hz ArH), 8.38 (s, 1H, C-4 of coumarin). ESI-MS 446 $[M-H]^+$; *Anal*. Calcd for $C_{18}H_{12}Cl_2N_6O_2S$: C, 48.33; H, 2.70; N, 18.79; S, 7.17. Found: C, 48.37; H, 2.74; N, 18.84; S, 7.21%.

3-[3-(3,5-Dimethyl-pyrazol-1-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl]-6-nitro-chromen-2-one (4i). Color: yellow solid; Yield 80%; mp 240–242°C; IR (KBr, υ max/cm^{-1}): 1755 (lactone CO), 1590 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3 of pyrazole), 2.28 (s, 3H, CH_3 of pyrazole), 4.36 (s, 2H, thiadiazine), 6.18 (s, 1H, pyrazole), 7.35(t, 1H, J = 7.8 Hz, ArH), 7.42 (d, 2H, J = 7.6 Hz ArH), 8.41 (s, 1H, C-4 of coumarin). *Anal*. Calcd for $C_{18}H_{13}N_7O_4S$: C, 51.06; H, 3.09; N, 23.16; S, 7.57. Found: C, 51.12; H, 3.10; N, 23.14; S, 7.62%.

Acknowledgment. The authors are thankful to CSIR, New Delhi, India, for providing financial support.

REFERENCES AND NOTES

[1] Chadha, V. K.; Ranwa, N. S.; Dadheech, P. K. J. Phytol Res 1998, 11, 201.
[2] Sakata, M.; Shirakawa, Y.; Kamata, N.; Hiroshino, Y. S.; Jie, O. Y. J. Heterocycl Chem 2000, 37, 269.
[3] Nadkarni, B. A.; Kamat, V. R.; Khadse, B. G. Arzneim. Forsch 2001, 51, 569.
[4] Holla, B. S.; Akberali, P. M.; Shivananda, M. K. Farmaco 2001, 56, 919.
[5] Holla, B. S.; Rao, B. S.; Sarojini, B. K.; Akberali, P. M.; Kumari, N. S. Eur J Med Chem 2006, 41, 657.
[6] Jin, J. Y.; Zhang, L. X.; Zhang, A. J.; Lei, X. X.; Zhu, J. H. Molecules 2007, 12, 1596.
[7] Holla, B. S.; Sarojini, B.; Rao, S. B.; Akberali, P. M.; Kumari, N. S.; Shetty, V. IL Farmaco 2001, 56, 565.
[8] Mathew, V.; Keshavayya, J.; Vaidya, V. P.; Giles, D. Euro J Med Chem 2007, 42, 823.
[9] Varvaresou, A.; Siatra-Papastaikoudi, T.; Tsotinis, A.; Tsantili-Kakoulidou, A.; Vamvakides, A. Farmaco 1998, 53, 320.
[10] Kritsanida, M.; Mouroutsou, A.; Marakos, P.; Pouli, N.; Papakonstantinou-Garoufalias, S.; Pannecouque, C.; Witvrouw, M.; De Clercq, E. IL Farmaco 1996, 51, 659.
[11] El Khawass, S. M.; Khalli, M. A.; Hazzaa, A. A.; Bassiouny, H. A.; Loutfy, N. F. IL Farmaco 1989, 44, 703.
[12] Al-Masoudi, N. A.; Al-Soud, Y. A. Nucleosides Nucleotides Nucleic Acids 2008, 27, 1034.
[13] Arunkumar, S.; Ilango, K.; Bairam, R.; Ramalakshmi, N. Der Pharma Chemic 2009, 1, 70.
[14] Mir, I.; Siddiqui, M. T.; Comrie, A. Tetrahedron 1970, 26, 5235.
[15] Hester, J. B.; Ludens, J. H.; Emmert, D. E.; West, B. E. J Med Chem 1989, 32, 1157.
[16] Shah, M. H.; Mhasalkar, M. Y.; Palki, M. V.; Deliwala, C. V.; Sheth, U. K. J Pharm Sci 1969, 58, 1398.
[17] Demirbas, N.; Demirbas, A.; Karaoglu, S. A.; Çelik, E. Arkivoc 2005, 1, 75.
[18] Holla, B. S.; Veerendra, B.; Shivananda, M. K.; Poojary, B. Eur J Med Chem 2003, 38, 759.
[19] Pimerova, E. V.; Voronina, E. V., Pharm Chem J 2001, 35, 18.
[20] Janus, S. L.; Magdif, A. Z.; Erik, B. P.; Claus, N. Monatsh Chem 1999, 130, 1167.
[21] Sharma, R. N.; Sharma, K. P.; Dixit, S. N. Int J ChemTech Res 2010, 2, 800.
[22] Tewari, A. K.; Mishra, A. Bioorg Med Chem 2001, 9, 715.
[23] Park, H. J.; Lee, K.; Park, S. J.; Ahn, B.; Lee, J. C.; Cho, H. Y.; Lee, K. I. Bioorg Med Chem Lett 2005, 15, 3307.
[24] Bouabdallah, I.; M'barek, L. A.; Zyad, A.; Ramadan, A.; Zidane, I.; Melhaoui, A. Nat Prod Res 2006, 20, 1024.
[25] Michon, V.; Du Penhoat, C. H.; Tombret, F.; Gillardin, J. M.; Lepagez, F.; Berthon, L. Eur J Med Chem 1995, 30, 147.
[26] Nusrat, B. A.; Rabiul Islam, M. D. Bang J pharmacol, 2007, 2, 81.
[27] Monga Paramjeet, K.; Dipak, S.; Dubey, A. J Chem Pharm Res 2012, 4, 822.
[28] Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. Tetrahedron Asymmetr 2001, 12, 707.
[29] Wang, C. J.; Hsieh, Y. J.; Chu, C. Y.; Lin, Y. L.; Tseng, T. H. Cancer Lett 2002, 183, 163.
[30] Fan, G. J.; Mar, W.; Park, M. K.; Wook, C. E.; Kim, K.; Kim, S. Bioorg Med Chem Lett 2001, 11, 2361.
[31] Kayser, O.; Kolodziej, H. Planta Med 1997, 63, 508.
[32] Singer, L. A.; Kong, N. P. J Am Chem Soc 1966, 88, 5213.
[33] Nicholas, F.; Neil, P.. Lymphat Res Biol 2005, 3, 81.
[34] Zhu, J.; Bienaymé, H. Eds.; Multicomponent Reactions, Wiley-VCH: Weinheim, Germany, 2005.
[35] Rajeswar Rao, V.; Padmanabha Rao, T. V. Indian J Chem 1986, 25B, 413.