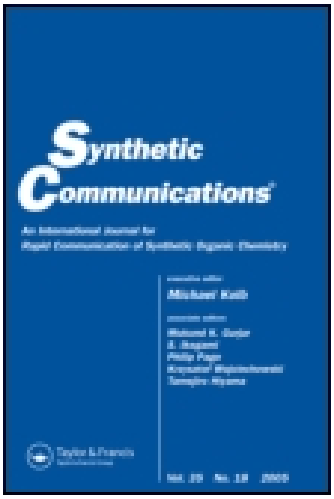

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient, One-Pot Synthesis of Triazolothiadiazinyl-pyrazolone and Pyrazolyl-triazolothiadiazine Derivatives via Multicomponent Reaction

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Accepted author version posted online: 30 Jan 2014.Published online: 29 Apr 2014.

To cite this article: Tewodros Birhanu Aychiluhim & Vedula Rajeswar Rao (2014) Efficient, One-Pot Synthesis of Triazolothiadiazinyl-pyrazolone and Pyrazolyl-triazolothiadiazine Derivatives via Multicomponent Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:10, 1422-1429, DOI: 10.1080/00397911.2012.721917

To link to this article: http://dx.doi.org/10.1080/00397911.2012.721917

Synthetic Communications®, 44: 1422–1429, 2014

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.721917

EFFICIENT, ONE-POT SYNTHESIS OF TRIAZOLOTHIADIAZINYL-PYRAZOLONE AND PYRAZOLYL-TRIAZOLOTHIADIAZINE DERIVATIVES VIA MULTICOMPONENT REACTION

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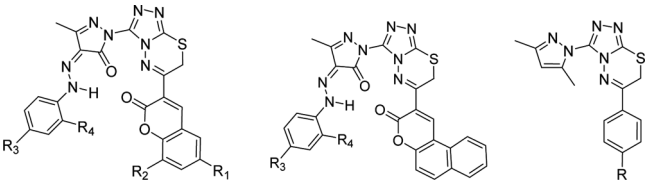
GRAPHICAL ABSTRACT



Abstract *A one-pot, multicomponent reaction of 3-(2-bromo acetyl)coumarins, 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol, and different derivatives of ethyl 2-(2-(aryl)hydrazono)-3-oxobutanoates provide an efficient and direct method for the synthesis of 4-(arylydrazono)-3-methyl-1-(6-(coumarin-3-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-1H-pyrazol-5(4H)-ones (**4a–h**). A similar methodology was also developed for the synthesis of pyrazolyl-triazolothiadiazines (**9a–f**) using acetyl acetone, 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol, and different derivatives of phenacylbromide. The resulting products were characterized by analytical and spectral data.*

Keywords Multicomponent reaction; pyrazole; pyrazolone; triazolothiadiazine

INTRODUCTION

Multicomponent reactions, involving succession of processes with at least three different substrates to generate complex molecular structures, have emerged as a powerful synthetic strategy in the field of organic synthesis. It would be worthy to conduct a series of simple steps in one pot, which would minimize the chemicals used, waste produced, and the reaction time consumed. Thus, great attention has been given to the development of cascade reactions.[1]

Coumarin derivatives have received significant attention as they possess several types of pharmacological properties, such as antibacterial, anticancer, anti-HIV, anticoagulant, antioxidant, and spasmolytic activities.[2]

Received June 25, 2012.

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Triazoles and their heterocyclic derivatives are attractive compounds that possess a wide range of biological activities.[3] In particular, the fused ring of triazoles and thiadiazines, called triazolothiadiazines, is important class of nitrogen bridgehead heterocyclic compounds with a wide range of activities. A recent literature survey revealed that a special attention was given to 1,2,4-triazolo[3,4-b][1,3,4]-thiadiazine derivatives, which are demonstrated to have promising biological activities such as antimicrobial, analgesic, antiviral, anti-HIV, CNS-stimulantory, and antifungal activites.[4–8]

Compounds containing pyrazolone ring systems have been consistently rewarded as promising molecules because of their broad-spectrum pharmacological activities such as antitubercular,[9] antimicrobial,[10] anticancer,[11] antiviral,[12] anti-inflammatory,[13] antipyretic,[13] analgesic,[14] ulcerogenic,[14] and lipid peroxidation activities.[14]

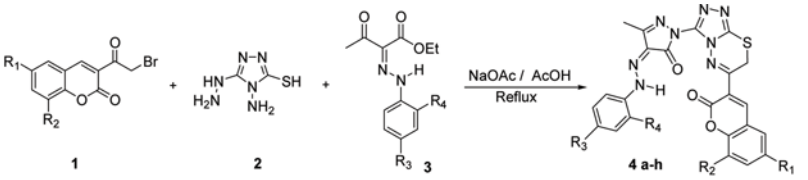
Furthermore, the synthesis of pyrazole and its analogs has also been a subject of consistent interest because of their wide range of applications in the pharmaceutical and agrochemical industries. Among their range of properties, they have widespread potential biological activities such as anti-inflammatory,[15] antipyretic,[16] antimicrobial,[17] antiviral,[18] antitumor,[19] anticonvulsant,[20] antihistaminic,[21] antidepressant,[22] insecticidal, and fungicidal activities.[23]

Extensive research efforts have been directed at the discovery of new heterocycles with appropriate pharmacological effects. Taking into account the importance of these heterocycles and starting materials for various applications, and in line with our interest to develop a multicomponent approach for the synthesis of sulfur- and nitrogen-containing heterocycles of biological importance, we became interested in developing efficient synthetic methods for the triazolothiadiazineyl-pyrazolone system incorporating coumarin derivatives and arylhydrazono moiety as substituents and the pyrazolyl-triazolothiadiazine system with substituted phenyl derivatives.

RESULTS AND DISCUSSION

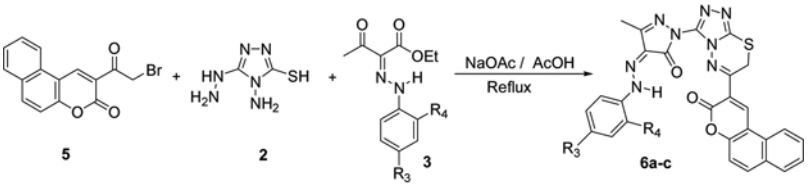
Earlier work from literature revealed that the syntheses of fused [1,2,4]triazolo-[1,3,4]thiadiazines mainly involve reactions of heterocyclic amino thiols with bifunctional reagents such as α-halo carbonyl compounds, dihalides, α-halo nitriles, and 1,3-diketones.[24–26] In addition, the literature survey clearly showed that ethylacetoacetate was reacted with hydrazine hydrate in the presence of ethanol to afford 3-methyl-1*H*-pyrazol-5(4*H*)–one.[27,28] 4-Amino-5-hydrazino-4*H*-[1,2,4]triazole-3-thiols can be considered as useful synthons in fusing to triazolothiadiazines. The amino and mercapto groups are ready-made nucleophilic centers for the synthesis of condensed heterocyclic rings.[29,30]

In the present work, various 3-(2-bromoacetyl)coumarin derivatives (**1** and **5**) were reacted with 4-amino-5-hydrazino-4*H*-[1,2,4]triazole-3-thiol (**2**) and ethyl-2-(2-arylhydrazono)-3-oxobutanoate (**3**) in acetic acid in the presence of sodium acetate to yield the compounds **4a–h** and **6a–c** (Scheme 1). 3-(3,5-Dimethyl-pyrazol-1-yl)-6-aryl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine analogs (**9a–f**) were synthesized by the reaction of acetyl acetone (**8**), 4-amino-5-hydrazino-4*H*-[1,2,4]triazole-3-thiol, with different phenacylbromides (**7**) under reflux for 3–4 h in methanol without using any base.



1 2 3 4 a-h

Compound	R_1	R_2	R_3	R_4	Yield (%)
4a	H	H	CH_3	H	89
4b	H	H	Cl	H	85
4c	H	H	NO_2	H	84
4d	H	H	H	H	88
4e	H	H	Cl	NO_2	84
4f	H	OCH_3	H	H	76
4g	H	OCH_3	NO_2	H	80
4h	Br	H	NO_2	H	86



5 2 3 6a-c

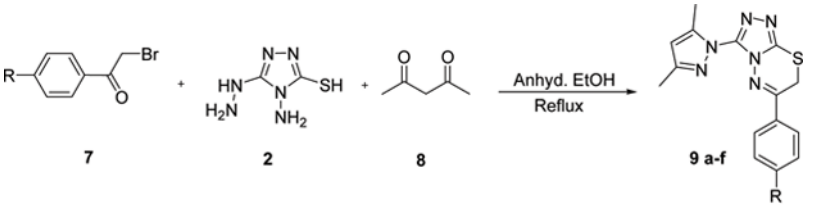
Compound	R_3	R_4	Yield (%)
6a	H	H	75
6b	Cl	H	76
6c	NO_2	H	71

Scheme 1. Syntheses of 4-(arylydrazono)-3-methyl-1-(6-(coumarin-3-yl)-7*H*-[1,2,4] triazolo[3,4-b][1,3,4]-thiadiazin-3-yl)-1*H*-pyrazol-5(4*H*)-ones.

During thiadiazine ring formation the highly nucleophilic mercapto group of the 4-amino-5-hydrazino-4*H*-[1,2,4]triazole-3-thiol attacks the carbon atom (-CH_2-Br) of 3-(2-bromoacetyl)coumarin to give a substituted intermediate. This undergoes further intramolecular cyclization, leading to the formation of a thiadiazine ring system.

Pyrazolone ring formation takes place by the condensation reaction between the hydrazino group of 3-(3-hydrazino-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-chromen-2-ones and ethyl-2-(2-arylhydrazono)-3-oxobutanoate (β-ketoester) to give end products **4a–h** and **6a–c**, whereas the intermediates 1-(6-aryl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)hydrazine react with acetyl acetone to give the compounds **9a–f** with pyrazole ring (Scheme 2).

The structures of all the newly synthesized compounds were characterized by analytical and spectral data. The IR spectra of compounds in Scheme 1 show absorption peak at 3117–3206 cm^{-1} that is attributed to (N-H) and prominent peaks at 1704–1744 cm^{-1} and 1674–1699 cm^{-1} corresponding to C=O bond-stretching frequencies of coumarin and pyrazolone respectively, and prominent peaks at 1539–1556 cm^{-1} attributed to C=N.



7 2 8 9 a-f

Compound	R_3	Yield (%)
9a	Cl	81
9b	OCH_3	82
9c	Br	87
9d	NO_2	84
9e	Phenyl	78
9f	H	90

Scheme 2. Synthesis of 3-(3,5-dimethyl-pyrazol-1-yl)-6-aryl-7*H*-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazine.

In the ^{1}H NMR spectra, the characteristic downfield signal at δ 13.02–14.19 attributed to the (-NH-N=C) peaks at δ 7.13–8.42 are attributed to the aromatic ring protons. The chemical shift of the S-CH_2 protons in the thiadiazine moiety appears at δ 4.36–4.43 (**4a–e** and **6a–c**), and δ 3.99–4.49 (**9a–f**).

The ^{13}C NMR spectrum of compound **4a**, for instance, exhibits the expected absorption peaks at δ 11.65, 20.50, 24.40, 116.26, 116.69, 118.19, 122.41, 125.08, 125.86, 129.92, 130.00, 133.94, 135.78, 139.00, 143.28, 144.87, 150.59, 153.98, 154.41, 156.94, and 158.55. The peaks at 11.65 and 20.50 are due to -CH_3 of pyrazolone and of phenyl respectively, the peak at 24.40 ppm is attributed to the S-CH_2 in the thiadiazine ring, and peaks at downfield chemical shifts 156.94 and 158.55 are due to carbonyl carbons of pyrazolone and coumarin respectively.

CONCLUSION

In this work an efficient methodology for the synthesis of the title compounds has been described. The methodology is a one-pot, three-component reaction leading to a novel bicyclic heterocyclic ring system. The method has advantages of good yield, short reaction time, and mild reaction conditions and is economical compared to the stepwise synthesis.

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources and were used without further purification unless otherwise stated. 3-(2-Bromoacetyl)-coumarin derivatives were prepared by literature procedure.[31] Ethyl-2-substituted hydrazone-3-oxobutyrates were prepared by following literature procedure.[32]

Melting-point values were determined in open capillaries with a "Stuart" melting-point apparatus (model SMP30) and were uncorrected. Infrared (IR) spectra in KBr pellets were recorded on a Bruker WM-4(X) FT-IR spectrophotometer (577 model). ^{1}H NMR spectra were recorded in dimethylsulfoxide (DMSO-d_6) and $CDCl_3$ on a Varian spectrometer (300 and 400 MHz) using tetramethylsilane

(TMS) as an internal standard. The mass spectra were recorded on a Perkin-Elmer instrument (SCIEX API- 2000, ESI) operating at 12.5 ev. CHNS analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by thin-layer chromatography (TLC) (E. Merck Mumbai, India). Iodine and ultraviolet (UV) chambers were used for visualizing spots.

General Procedure for the Synthesis of 5-Methyl-4-(aryl-hydrazono)-2-(6-(2-oxo-chromen-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-2,4-dihydro-pyrazol-3-one (4a–h, 6a–c)

3-(2-Bromoacetyl)coumarin (0.001 mol), 4-amino-5-hydrazino-4*H*-[1,2,4]-triazole-3-thiol (0.001 mol), and ethyl-2-substituted hydrazone-3-oxobutyrates (0.001 mol) were taken in 5 ml acetic acid, and then fused sodium acetate (0.002 mol) was added into the mixture. The mixture was refluxed for 3–5 h. After completion of reaction (monitored with thin-layer chromatography, TLC), the reaction mixture was allowed to cool. The solid obtained was filtered, washed with water, dried, and crystallized from suitable solvent to give the title compound.

4-(2-*p*-Tolylhydrazono)-3-methyl-1-(6-(2-oxo-2*H*-chromen-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5(4*H*)-one (4a)

3-(2-Bromoacetyl)-2*H*-chromen-2-one (0.001 mol), 4-amino-5-hydrazino-4*H*-[1,2,4]triazole-3-thiol (0.001 mol), and ethyl 2-(2-p-tolylhydrazono)-3-oxobutanoate (0.001 mol) were taken in 5 ml acetic acid, and then fused sodium acetate (0.002 mol) was added into the mixture. The mixture was refluxed for 4 h. The reaction mixture was cooled to rt. The solid was formed gradually. It was filtered, washed with water, dried, and recrystallized from acetic acid. Orange color solid; yield 87%; mp 176–179 °C; IR (KBr, υ_{max}, cm^{-1}): 3170 (N-H), 1722 (C=O, coumarin), 1678 (C=O, pyrazolone), 1539 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 3H, $-CH_3$), 2.31 (s, 3H, $-CH_3$ of pyrazolone), 4.36 (s, 2H, S-CH_2- of thiadiazine ring), 7.25 (d, 2H, $J = 8.7$ Hz, Ar-H), 7.40 (t, 1H, $J = 7.5$ Hz Ar-H), 7.49–7.57 (m, 3H, Ar-H), 7.70–7.75 (m, 1H, Ar-H), 7.87 (t, 1H, $J = 3.7$ Hz, Ar-H), 8.51 (s, 1H, C_4 proton of coumarin), 13.09 (s, 1H, -NH, D_2O, exchangeable). ^{13}C NMR (DMSO-d_6, δ ppm): 11.65, 20.50, 24.40, 116.26, 116.69, 118.19, 122.41, 125.08, 125.86, 129.92, 130.00, 133.94, 135.78, 139.00, 143.28, 144.87, 150.59, 153.98, 154.41, 156.94, 158.55. MS (ES) m/z 499 ($[M + H]^+$). Anal. calcd. for $C_{24}H_{18}N_8O_3S$: C, 57.82; H, 3.64; N, 22.48; S, 6.43. Found: C, 57.86; H, 3.60; N, 22.51; S, 6.48.

General Procedure for the Synthesis of 3-(3,5-Dimethyl-pyrazol-1-yl)-6-aryl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9a–f)

Phenacyl bromide (0.001 mol), 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol (0.001 mol), and acetyl acetone (0.001 mol), were taken in 5 ml absolute ethanol. The mixture was refluxed for 3–4 h. After completion of reaction (monitored by TLC), the reaction mixture was allowed to cool. The solid obtained was filtered. In cases where no solid separation occurred upon cooling, the reaction mixture

was poured into ice-cold water. The solid obtained was filtered, dried, and recrystallized.

6-(4-Chlorophenyl)-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9a)

2-Bromo-1-(4-chlorophenyl)ethanone (0.001 mol), 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol (0.001 mol), and acetyl acetone (0.001 mol), were taken in 5 ml absolute ethanol. The mixture was refluxed for 3 h. The solid obtained was filtered. The solid obtained was filtered, dried, and recrystallized. Pale yellow color, solid; yield 81%; mp 199–201 °C; IR (KBr, υ_{max}, cm^{-1}): 1656 (C=N), 1583 (C=C), 1477 (N=C-S); ^{1}H NMR (300 MHz, $CDCl_3$): 2.29 (s, 3H, -CH_3), 2.44 (s, 3H, $-CH_3$), 3.98 (s, 2H, S-CH_2- of thiadiazine ring), 6.90 (s, 1H, pyrazole proton), 7.45 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.76 (d, 2H, $J = 8.7$ Hz, Ar-H). ^{13}C NMR (DMSO-d_6, δ ppm): 10.80, 13.22, 22.96, 107.52, 129.18, 129.26, 131.89, 136.99, 142.45, 142.96, 146.39, 150.98, 155.48. MS (ES): m/z 344.9 ($[M + H]^+$). Anal. calcd. for $C_{15}H_{13}ClN_6S$: C, 52.25; H, 3.80; N, 24.37; S, 9.30. Found: C, 52.29; H, 3.85; N, 24.34; S, 9.34.

ACKNOWLEDGMENT

The authors are thankful to the director, National Institute of Technology, Warangal, A.P., India for providing support.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

1. Hongwei, J.; Bingwei, Z.; Zhi, W.; Yang, S.; Yanguang, W. One-pot synthesis of substituted indolines via a copper-catalyzed sequential multi-component/C N coupling reaction. *Tetrahedron.* **2011**, *67*, 1178–1182.
2. (a) Marshall, M. E.; Kervin, K.; Benefield, C.; Umerani, A.; Albainy-Jenei, S.; Zhao, Q.; Khazaeli, M. B. Growth-inhibitory effects of coumarin (1,2-benzopyrone) and 7-hydroxycoumarin on human malignant cell lines in vitro. *J. Cancer Res. Clin. Oncol.* **1994**, *120*, S3–S10; (b) Kostova, I.; Momekov, G.; Zaharieva, M.; Karaivanova, M. Cytotoxic activity of new lanthanum(III) complexes of bis-coumarins. *Eur. J. Med. Chem.* **2005**, *40*, 542–551; (c) Manolov, I.; Maichle-Moessmer, C.; Danchev, N. Synthesis, structure, toxicological, and pharmacological investigations of 4-hydroxycoumarin derivatives. *Eur. J. Med. Chem.* **2006**, *41*, 882–889; (d) Hamdi, N.; Puerta, C.; Valerga, P. Synthesis, structure, antimicrobial, and antioxidant investigations of dicoumarol and related compounds. *Eur. J. Med. Chem.* **2008**, *43*, 2541–2548; (e) Stanchev, S.; Momekov, G.; Jensen, F.; Manolov, L. Synthesis, computational study and cytotoxic activity of new 4-hydroxycoumarin derivatives. *Eur. J. Med. Chem.* **2008**, *43*, 694–706; (f) Angerer, E. V.; Kager, M.; Maucher, A. Antitumour activity of coumarin in prostate and mammary cancer models. *J. Cancer Res. Clin. Oncol.* **1994**, *120*, S14–S16.

3. Al-Masoudi, I. A.; Al-Soud, Y. A.; Al-Salihi, N. J.; Al-Masoudi, N. A. 1,2,4-Triazoles: Synthetic approaches and pharmacological importance. *Chem Heterocycl Comp.* **2006**, *42*, 1377–1403.
4. Chadha, V. K.; Ranwa, N. S.; Dadheech, P. K. Synthesis and screening of biological activity of triazolothiadiazines and triazolothiadiazoles. *J. Phytol. Res.* **1998**, *11*, 201–202.
5. (a) Sakata, M.; Shirakawa, Y.; Kamata, N.; Hiroshino, Y. S.; Jie, O. Y. Synthesis and antibacterial activity of some new s-triazolo[3,4-b]-1,3,4-thiadiazine derivatives. *J. Heterocycl. Chem.* **2000**, *37*, 269–271; (b) Hui, X. P.; Zhang, Y.; Xu, P. F.; Wang, Q.; Zhang, Q.; Zhang, Z. Y. Syntheses and antibacterial activities of novel 3-substituted-6-(4-chlorophenyl)-7-(1H-1,2,4-triazole-1-yl)-1′,2’,4′-triazolo[3,4-b]-1″,3″,4″-thiadiazines. *Chin. J. Org. Chem.* **2005**, *25*, 700–704.
6. Nadkarni, B. A.; Kamat, V. R.; Khadse, B. G. Synthesis and anthelmintic activity of 3,6-disubstituted-7H-s-triazolo[3,4-b][1,3,4] thiadiazines. *Arzneim. Forsch.* **2001**, *51*, 569–573.
7. (a) Holla, B. S.; Akberali, P. M.; Shivananda, M. K. Studies on nitrophenyl furan derivatives, part XII: Synthesis, characterization, antibacterial, and antiviral activities of some nitrophenyl-furfurylidene-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines. *Farmaco.* **2001**, *56*, 919–927; (b) Holla, B. S.; Rao, B. S.; Sarojini, B. K.; Akberali, P. M.; Kumari, N. S. Synthesis and studies on some new fluorine-containing triazolothiadiazines as possible antibacterial, antifungal, and anticancer agents. *Eur. J. Med. Chem.* **2006**, *41*, 657–663.
8. (a) Turan-Zitouni, G.; Kaplancikli, Z. A.; Erol, K.; Kiliç, F. S. Synthesis and analgesic activity of some triazoles and triazolothiadiazines. *Farmaco.* **1999**, *54*(4), 218–23; (b) Kritsanida, M.; Mouroutsou, A.; Marakos, P.; Pouli, N.; Papakonstantinou-Garoufalias, S.; Pannecouque, C.; Witvouw, M.; De Clercq, E. Synthesis and antiviral activity evaluation of some new 6-substituted3-(1-adamantyl)-1,2,4-triazolo[3,4-*b*] [1,3,4]thiadiazoles. *Farmaco* **2002**, *57*, 253.
9. Castagnolo, D.; De Logu, A.; Radi, M.; Bechi, B.; Manetti, F.; Magnani, M.; Supino, S.; Meleddu, R.; Chisu, L.; Botta, M. Synthesis, biological evaluation, and SAR study of novel pyrazole analogues as inhibitors of Mycobacterium tuberculosis. *Bioorg. Med. Chem.* **2008**, *16*(18), 8587–8591.
10. Ragavan, R. V.; Vijayakumar, V.; Kumari, N. S. Synthesis of some novel bioactive 4-oxy/thio substituted-1H-pyrazol-5(4H)-ones via efficient cross-Claisen condensation. *Eur. J. Med. Chem.* **2009**, *44*(10), 3852–3857.
11. (a) Brana, M. F.; Gradillas, A.; Ovalles, A. G.; Lopez, B.; Acero, N.; Llinares, F. Synthesis and biological activity of N,N-dialkylaminoalkyl-substituted bisindolyl and diphenyl pyrazolone derivatives. *Bioorg. Med. Chem.* **2006**, *14*(1), 9–16; (b) Kim, K. R.; Kwon, J. L.; Kim, J. S.; Zaesung, N.; Kim, H. R.; Cheon, H. G. EK-6136 (3-methyl-4-(O-methyl-oximino)-1-phenylpyrazolin-5-one): A novel Cdc25B inhibitor with antiproliferative activity. *Eur. J. Pharmacol.* **2005**, *528*, 37–42.
12. Fan, X.; Zhang, X.; Zhou, L.; Keith, K. A.; Kernb, E. R.; Torrencea, P. F. A pyrimidine-pyrazolone nucleoside chimera with potent in vitro anti-orthopoxvirus activity. *Bioor. Med. Chem. Lett.* **2006**, *16*, 3224.
13. (a) Ismail, M. M. F.; Ammar, Y. A.; El -Zahaby, H. S. A.; Eisa, S. I.; Barakat, S. E. Synthesis of novel 1-pyrazolylpyridin-2-ones as potential anti-inflammatory and analgesic agents. *Arch. Pharm. Life. Sci.* **2007**, *340*, 476; (b) El-Hawash, A. M.; El-Sayed, A. M. B.; El-Ashmawey, I. M. Nonsteroidal antiinflammatory agents, part 2: Anti-inflammatory, analgesic, and antipyretic activity of some substituted 3-pyrazolin-5-ones and 1,2,4,5,6,7-3H-hexahydroindazol-3-ones. *Eur. J. Med. Chem.* **2006**, *41*, 155.
14. Mohd, A.; Kumar, S. Synthesis and anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation activities of 3,5-dimethyl pyrazoles,3-methyl pyrazole-5-ones and 3,5-disubstituted pyrazolines. *Indian J. Chem.* **2005**, *44B*, 2532.

15. Tewari, A. K.; Mishra, A. Synthesis and anti-inflammatory activities of N4, N5-disubstituted-3-methyl-1H-pyrazolo[3,4-c]pyridazines. *Bioorg. Med. Chem.* **2001**, *9*, 715–718.
16. Wiley, R. H.; Wiley, P. *Pyrazolones, Pyrazolidones and Derivatives*; John Wiley and Sons: New York, 1964.
17. Pimerova, E. V.; Voronina, E. V. Antimicrobial activity of pyrazoles and pyridazines obtained by interaction of 4-aryl-3-arylhydrazono-2,4-dioxobutanoic acids and their esters with hydrazines. *Pharm. Chem. J.* **2001**, *35*, 18–20.
18. Janus, S. L.; Magdif, A. Z.; Erik, B. P.; Claus, N. Synthesis of triazenopyrazole derivatives as potential inhibitors of HIV-1. *Monatsh. Chem.* **1999**, *130*, 1167–1174.
19. (a) Park, H. J.; Lee, K.; Park, S.; Ahn, B.; Lee, J. C.; Cho, H. Y.; Lee, K. I. Identification of antitumor activity of pyrazole oxime ethers. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3307–3312; (b) Bouabdallah, I.; M'barek, L. A.; Zyad, A.; Ramadan, A.; Zidane, I.; Melhaoui, A. Anticancer effect of three pyrazole derivatives. *Nat. Prod. Res.* **2006**, *20*, 1024–1030.
20. Michon, V.; Du Penhoat, C. H.; Tombret, F.; Gillardin, J. M.; Lepagez, F.; Berthon, L. Preparation, structural analysis, and anticonvulsant activity of 3-and 5-aminopyrazole N-benzoyl derivatives. *Eur. J. Med. Chem.* **1995**, *30*(2), 147–155.
21. Yildirim, I.; Ozdemir, N.; Akçamur, Y.; Dinçer, M.; Andaç, O. 4-Benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid methanol solvate. *Acta Cryst.* **2005**, *E61*, 256–258.
22. Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J.; Defelice, A. F.; Feigenson, M. E. 3,4-Diphenyl-1H-pyrazole-1-propanamine antidepressants. *J. Med. Chem.* **1985**, *28*, 256–260.
23. Chu, C. K.; Cutler, J. Chemistry and antiviral activities of acyclonucleosides. *J. Heterocycl. Chem.* **1986**, *23*, 289–319.
24. Khanum, S. A.; Shashikanth, S.; Umesha, S.; Kavitha, R. Synthesis and antimicrobial study of novel heterocyclic compounds from hydroxybenzophenones. *Eur. J. Med. Chem.* **2005**, *40*, 1156–1162.
25. Jin, J. Y.; Zhang, L. X.; Chen, X. X.; Zhang, A. J.; Zhang, H. L. Synthesis and biological activities of 6-aryl-3-(3-hydroxy-propyl)-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines. *Molecules* **2007**, *12*, 297–303.
26. Farghaly, A. R.; De Clercq, E.; El-Kashef, H. Synthesis and antiviral activity of novel [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles, [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines, and [1,2,4]triazolo[3,4-b][1,3,4] thiadiazepines. *Arkivoc* **2006**, *10*, 137–151.
27. Mohareb, R. M.; Ibrahim, R. A. Novel synthesis of pyridazine and pyrazole derivatives and their anti-tumor evaluations. *Int. J. Appl. Biol. Pharm. Technol.* **2011**, *2*(1), 0976–4550.
28. Subramanyam, S.; Raja, S.; Jayaveera, K.; Sunil Kumar, K. Synthesis, characterization, and biological activity of 1,8-napthyridine nucleus linked with pyrazolinone, pyrazole, isoxazolinone, and isoxazole derivatives. *Int. J. Innovative Pharm. Res.* **2012**, *3*(1), 187–193.
29. El-Khawass, S. M.; Habib, N. S. Synthesis of 1,2,4-triazole, 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole, and 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine derivatives of benzotriazole. *J. Het. Chem.* **1989**, *26*(1), 177–180.
30. Shawali, A. S.; Zeid, I. F.; Abdelkader, H.; Elsherbini, A. A.; Altalbawy, F. M. A. Synthesis, acidity constants, and tautomeric structure of 7-arylhydrazono [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines in ground and excited states. *J. Chin. Chem. Soc.* **2001**, *48*, 65–72.
31. Rajeswar Rao, V.; Padmanabha Rao, T. V. Studies of thiazolyl imidazolyl-2H-1-benzopyran-2-ones. *Indian J. Chem.* **1986**, *25B*, 413–415.
32. Rajput, A. P.; Rajput, S. S. Synthesis and microbial screening of seven-membered heterocyclic ring compounds from 1,2-diaminobenzene. *Int. J. Pharm. Tech. Res.* **2009**, *1*(3), 900–904.