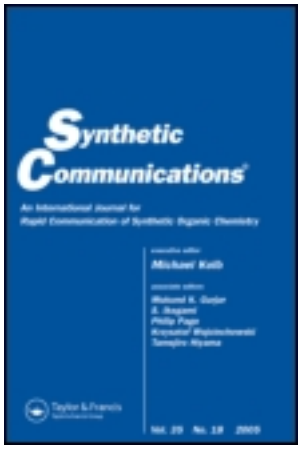

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Synthesis of Aryl and Heteryl 1,3,4-Thiadiazinyl-phthalazine-1,4-dione Derivatives via a Multicomponent Approach

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SYNTHESIS OF ARYL AND HETERYL 1,3,4-THIADIAZINYL-PHTHALAZINE-1,4-DIONE DERIVATIVES VIA A MULTICOMPONENT APPROACH

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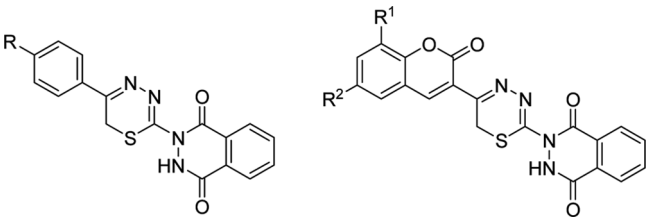
GRAPHICAL ABSTRACT



Abstract *An expeditious one-pot method has been developed for the synthesis of aryl, heteryl thiadiazinyl-phthalazine-1,4-diones via a multicomponent approach. Reaction of phenacyl bromides with thiocarbohydrazide and phthalic anhydride afforded corresponding aryl thiadiazinyl-phthalazine-1,4-diones. Similarly, reaction of 3-(2-bromoacetyl)coumarins with thiocarbohydrazide and phthalic anhydride afforded required heteryl thiadiazinyl-phthalazine-1,4-diones under the same reaction conditions in excellent yields. The structure of all the synthesized compounds was confirmed from their analytical and spectral data.*

Keywords 3-(2-Bromoacetyl)coumarins; one-pot reaction; phenacyl bromides; phthalic anhydride; thiocarbihydrazide

INTRODUCTION

Phthalazine derivatives have been widely used as therapeutic agents because of their anticonvulsant, vasorelaxant, anti-inflammatory, antipyretic, antihypertensive, and bronchodilatory effects.[1–3] In derivatives of phthalazines, 2,3-dihydrophthalazine-1(4*H*), 4-diones are very important class of intermediates in the synthesis of drug molecules such as the antihypertensive agent *dihydralazine* (1,4-dihydrazinophthalazine).[4] Phthalazinediones are usually obtained by condensation of appropriate phthalic acid derivatives such as esters or anhydrides with hydrazine.[5]

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Moreover, these compounds have attracted considerable attention because they exhibit interesting chemiluminescence phenomena,[6] they have pronounced dienophilic properties,[7] and they can be used as precursors for the preparation of benzocyclobutene-1,2-diones, which, in turn, represent useful synthons.[8] Similarly, heterocycles containing a phthalazine moiety also show some pharmacological and biological activities.[9–11] Some examples are [1,2,3]triazolo[4,5-*g*]phthalazine-4, 9-diones,[12] pyrazolo[1,2-b]phthalazines,[13,14] and [5,6]benza-3a,7a-diazaindanes.[15]

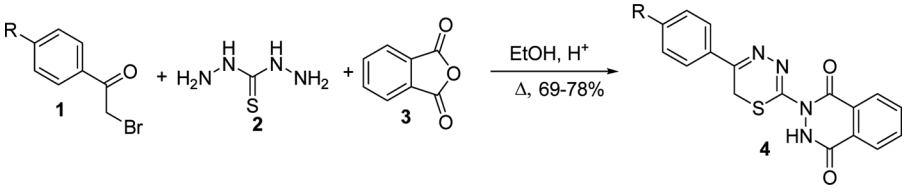
1,3,4-Thiadiazines were biologically active compounds. Many of these derivatives were important matrix metalloproteinase inhibitors.[16] They have shown excellent cardiotonic and hypertensive activities.[17,18] They act as phosphodiesterase IV inhibitors and may be used for treatment of tumors and acquired immune deficiency syndrome (AIDS).[19] These derivatives may be used in agriculture as pesticides and insecticides.[20] Some of these derivatives act as photographic magenta couplers.[21]

Based on these results and as a part of our research program in the synthesis of novel heterocyclic systems,[22–24] we report the synthesis of a novel heterocyclic system, 1,3,4-thiadiazinyl-phthalazine-1,4-dione, via multicomponent approach.

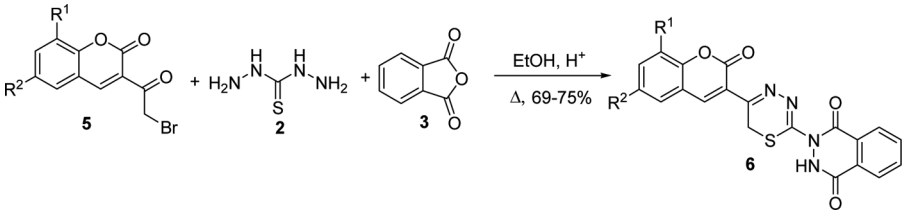
RESULTS AND DISCUSSION

Reaction of an equimolar mixture of phenacyl bromide, thiocarbohydrazide, and phthalic anhydride in anhydrous ethanol and a catalytic amount of acetic acid at 60–65 °C gave a novel bicyclic ring system, 2,3-dihydro-2-(5-aryl-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-diones (**4a–f**), in good yields (Scheme 1). In this one-pot reaction, two heterocyclic ring systems (thiadiazine and phthalazine-1,4-dione) were developed simultaneously. In the formation of products, it is believed that the thiocarbohydrazide first reacts with phenacyl bromide to give an uncyclized intermediate by the elimination of HBr, which further undergoes cyclization by eliminating water to give hydrazino-thiadiazine derivative. This, on reaction with phthalic anhydride, gave 1,3,4-thiadiazinyl-phthalazine-1,4-dione in good yields. The structure of the compounds was confirmed from their analytical and spectral data.

For example, the infrared (IR) spectrum of compound **4b** showed two strong absorption peaks at 3233 cm^{-1} and 1663 cm^{-1} for NH and amide carbonyl respectively. The ^1H NMR spectrum of compound **4b** showed sharp singlets at δ 2.35 and δ 3.95 for methyl and methelene of thiadiazine, respectively. A broad singlet at for NH is also observed at δ 8.76, which is exchangeable with D_2O. These spectral data clearly prove the structures of the products **4a–f**.



Scheme 1. Synthesis of 2,3-dihydro-2-(5-aryl-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-diones. **4a**: R = Cl; **4b**: R = Me; **4c**: R = OMe; **4d**: R = H; **4e**: R = NO_2; and **4f**: R = Ph.



Scheme 2. One-pot synthesis of 2,3-dihydro-2-(5-(2-oxo-2*H*-chromen-3-yl)-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-diones. **6a**: $R^1 = R^2 = H$; **6b**: 5,6-benzoanalouge of **6a**; **6c**: $R^1 = H$, $R^2 = Cl$; **6d**: $R^1 = R^2 = Cl$; and **6e**: $R^1 = R^2 = Br$.

These results encouraged us to test this one-pot reaction with 3-(2-bromoacetyl)coumarin in place of phenacyl bromides. Reaction of an equimolar mixture of 3-(2-bromoacetyl)coumarin, thiocarbohydrazide, and phthalic anhydride in anhydrous ethanol and catalytic amount of acetic acid at 60–65 °C also gave a novel tricyclic ring system, 2,3-dihydro-2-(5-(2-oxo-2*H*-chromen-3-yl)-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-diones (**6a–e**), in good yields (Scheme 2). The IR spectrum of compound **6a** showed absorption peaks at 3443 cm^{-1}, 1729 cm^{-1}, and 1680 cm^{-1} attributed to NH, lactone carbonyl, and amide carbonyl, respectively. The ^1H NMR spectrum of compound **6a** also showed sharp singlets at δ 3.96 and δ 8.25 for methylene of thiadiazine ring and C-4 proton of comarin and a broad singlet is observed at δ 8.33 for NH, which is exchangeable with D_2O.

In conclusion, we have developed a one-pot reaction for the synthesis of aryl and heteryl 1,3,4-thiadiazinyl-phthalazine-1,4-dione derivatives via a multicomponent approach using readily available starting materials. These highly functionalized derivatives may be of interest for pharmaceutical purposes yet to be explored.

EXPERIMENTAL

All the reagents and solvents were pure, purchased from commercial sources, and used without further purification unless otherwise stated. 3-(2-Bromoacetyl)coumarins[25] were prepared according to literature procedure. Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India) and were uncorrected. CHNS analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by thin-layer chromatographic (TLC) plates (E. Merck Mumbai, India). IR spectra (KBr) were recorded on a Bruker Optics (model Tensor 27) spectrometer. ^1H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using tetramethylsilane (TMS) as standard. Mass spectra (ESI-MS) were determined on a Perkin-Elmer (SCIEX API-2000, ESI) at 12.5 ev.

General Procedure for the Synthesis of Aryl and Heteryl 1,3,4-Thiadiazinyl-phthalazine-1,4-diones

An equimolar mixture of phenacyl bromide or 3-(2-bromoacetyl)coumarin, thiocarbohydrazide, and phthalic anhydride was taken in anhydrous ethanol

containing a catalytic amount of acetic acid. The reaction mixture was heated at 60–65 °C for about 2–3 h and cooled to room temperature. The yellow solid obtained was filtered, washed with water, and recrystallized from aqueous ethanol.

2-(5-(4-Chlorophenyl)-6*H*-1,3,4-thiadiazin-2-yl)-2,3-dihydrophthalazine-1,4-dione (4a)

Yield 70%; mp 271–273 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3423 (NH), 1656 (amide, −C=O), 1597 (−C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 2H, CH_2), 7.40–7.67 (m, 4H, ArH), 7.71–7.88 (m, 4H, ArH), 8.74 (s, 1H, NH, D_2O exchangeable); ESI-MS 370 [M^+]; ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 22.6, 109.8, 116.3, 121.6, 125.2, 128.1, 129.0, 130.7, 131.0, 136.5, 137.2, 139.1, 149.2, 157.9, 167.4. Anal. calcd. for $C_{17}H_{11}ClN_4O_2S$: C, 55.06; H, 2.99; N, 15.11, Found: C, 54.96; H, 2.94; N, 15.15%.

2,3-Dihydro-2-(5-*p*-tolyl-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-dione (4b)

Yield 78%; mp > 300 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3232 (NH), 1663 (amide, −C=O), 1598 (−C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, Me), 3.95 (s, 2H, CH_2), 7.14–7.18 (m, 2H, ArH), 7.60–7.88 (m, 6H, ArH), 8.76 (s, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99, Found: C, 61.59; H, 3.94; N, 15.88%.

2,3-Dihydro-2-(5-(4-methoxyphenyl)-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-dione (4c)

Yield 78%; mp 282–284 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3446 (NH), 1665 (amide, −C=O), 1595 (−C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H, OMe), 4.0 (s, 2H, CH_2), 6.59–6.66 (m, 2H, ArH), 6.96–6.98 (m, 3H, ArH), 8.07–8.10 (m, 3H, ArH), 8.30 (s, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{18}H_{14}N_4O_3S$: C, 59.01; H, 3.85; N, 15.29, Found: C, 58.95; H, 3.80; N, 15.22%.

2,3-Dihydro-2-(5-phenyl-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-dione (4d)

Yield 71%; mp 222–224 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3420 (NH), 1656 (amide, −C=O), 1601 (−C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 2H, CH_2), 7.44–7.46 (m, 4H, ArH), 7.71–7.86 (m, 5H, ArH), 8.86 (s, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{17}H_{12}N_4O_2S$: C, 60.70; H, 3.60; N, 16.66, Found: C, 60.65; H, 3.49; N, 16.58%.

2,3-Dihydro-2-(5-(4-nitrophenyl)-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-dione (4e)

Yield 69%; mp 234–236 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3428 (NH), 1658 (amide, −C=O), 1597 (−C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (s, 2H, CH_2),

7.89–7.92 (m, 4H, ArH), 8.29–8.31 (m, 4H, ArH), 8.97 (s, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{17}H_{11}N_5O_4S$: C, 53.54; H, 2.91; N, 18.36, Found: C, 53.50; H, 2.87; N, 18.30%.

2-(5-Biphenyl-4-yl-6*H*-[1,3,4]thiadiazin-2-yl)-2,3-dihydro-phthalazine-1,4-dione (4f)

Yield 76%; mp 251–253 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3427 (NH), 1649 (amide, −C=O), 1606 (−C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 2H, CH_2), 7.45–7.83 (m, 13H, ArH), 8.95 (s, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{23}H_{16}N_4O_2S$: C, 66.97; H, 3.91; N, 13.58, Found: C, 66.91; H, 3.87; N, 13.51%.

2,3-Dihydro-2-(5-(2-oxo-2*H*-chromen-3-yl)-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-dione (6a)

Yield 73%; mp 206–208 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3443 (NH), 1729 (lactone, −C=O), 1680 (amide, −C=O), 1602 (−C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 2H, CH_2), 7.36–7.39 (m, 2H, ArH), 7.60–7.63 (m, 2H, ArH), 7.74–8.05 (m, 4H, ArH), 8.25 (s, 1H, C_4 of comarin), 8.33 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$-d_6): 23.9, 111.2, 114.5, 116.4, 117.8, 124.6, 126.8, 128.3, 128.8, 131.2, 132.6, 134.0, 134.8, 138.5, 142.5, 143.6, 152.2, 158.8, 163.2, 166.8. ESI-MS 405 [M + H]. Anal. calcd. for $C_{20}H_{12}N_4O_4S$: C, 59.40; H, 2.99; N, 13.85, Found: C, 59.34; H, 2.91; N, 13.79%.

2,3-Dihydro-2-(5-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)-6*H*-1,3,4-thiadiazin-2-yl)phthalazine-1,4-dione (6b)

Yield 75%; mp 152–154 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3424 (NH), 1715 (lactone, −C=O), 1655 (amide, −C=O), 1595 (−C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 4.11 (s, 2H, CH_2), 7.44–8.12 (m, 10H, ArH), 8.75 (s, 1H, C_4 of comarin), 9.0 (s, 1H, NH, D_2O exchangeable). ESI-MS 454 [M^+]. Anal. calcd. for $C_{24}H_{14}N_4O_4S$: C, 63.43; H, 3.11; N, 12.33, Found: C, 63.37; H, 3.18; N, 12.27%.

2-(5-(6-Chloro-2-oxo-2*H*-chromen-3-yl)-6*H*-1,3,4-thiadiazin-2-yl)-2,3-dihydrophthalazine-1,4-dione (6c)

Yield 69%; mp 185–187 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3426 (NH), 1735 (lactone, −C=O), 1660 (amide, −C=O), 1601 (−C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 2H, CH_2), 7.38–7.59 (m, 4H, ArH), 7.69–8.01 (m, 2H, ArH), 8.13 (d, 1H, $J = 2.8$ Hz, Hz, ArH), 8.96 (s, 1H, C_4 of comarin), 10.44 (s, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{20}H_{11}ClN_4O_4S$: C, 54.74; H, 2.53; N, 12.77, Found: C, 54.68; H, 7.94; N, 12.70%.

2-(5-(6,8-Dichloro-2-oxo-2*H*-chromen-3-yl)-6*H*-1,3,4-thiadiazin-2-yl)-2,3-dihydrophthalazine-1,4-dione (6d)

Yield 72%; mp 182–184 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3225 (NH), 1742 (lactone, −C=O), 1666 (amide, −C=O), 1595 (−C=N); ^1H NMR (400 MHz, $CDCl_3$): δ

3.96 (s, 2H, CH_2), 7.38–7.59 (m, 4H, ArH), 7.87 (d, 1H, $J = 2.8$ Hz, ArH), 8.13 (d, 1H, $J = 2.4$ Hz, ArH), 8.96 (s, 1H, C_4 of comarin), 9.78 (s, 1H, NH, D_2O, exchangeable). Anal. calcd. for $C_{20}H_{10}Cl_2N_4O_4S$: C, 50.75; H, 2.13; N, 11.84, Found: C, 50.69; H, 2.10; N, 11.79%.

2-(5-(6,8-Dibromo-2-oxo-2*H*-chromen-3-yl)-6*H*-1,3,4-thiadiazin-2-yl)-2,3-dihydrophthalazine-1,4-dione (6e)

Yield 75%; mp 168–170 °C; yellow; IR (KBr, υ*max*, cm^{-1}): 3432 (NH), 1719 (lactone, −C=O), 1647 (amide, −C=O), 1597 (−C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 2H, CH_2), 7.46–7.60 (m, 3H, ArH), 7.81 (d, 1H, $J = 7.6$ Hz, ArH), 8.15–8.18 (m, 2H, ArH), 8.25 (s, 1H, C_4 of comarin), 10.46 (s, 1H, NH, D_2O, exchangeable). Anal. calcd. for $C_{20}H_{10}Br_2N_4O_4S$: C, 42.73; H, 1.79; N, 9.97, Found: C, 42.68; H, 1.75; N, 9.92%.

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REFERENCES

1. Tsoungas, P. G.; Searcey, M. A convenient access to benzo-substituted phthalazines as potential precursors to DNA intercalators. *Tetrahedron Lett.* **2001**, *42*, 6589–6592.
2. Sivakumar, R.; Gnanasam, S. K.; Ramachandran, S.; Leonard, J. T. Pharmacological evaluation of some new 1-substituted-4-hydroxyphthalazines. *Eur. J. Med. Chem.* **2002**, *37*, 793–801.
3. Murray, B. G.; Parsons, D. G.; Turner, A. F. British Patent **1968**, *1133*, 406.
4. Druey, J.; Ringier, B. H. Hydrazinderivate der phtalazin- und pyridazinreihe. *Helv. Chim. Acta.* **1951**, *34*, 195–210.
5. Patel, N. R. *In Condensed Pyridazines Including Cinnolines and Phthalazines*; R. N. Castle (Ed.); Wiley: New York, 1973; p. 446.
6. Gundermann, K.-D.; Fiege, H.; Klockenbring, G. Constitution and chemiluminescence, IV: Chemiluminescence of diazaquinones: Mechanism for the chemiluminescent reaction of cyclic diacylic hydrazides. *Liebigs Ann. Chem.* **1970**, *738*, 140–160.
7. Gómez Contreras, F.; Lora-Tamayo, M.; Sanz, A. M. Diazapolycyclic compounds, XXVIII: The reaction of acetylated terpenoids with diazaquinones. *Heterocycles* **1989**, *28*, 791–803.
8. Gould, K. J.; Hacker, N. P.; McOmie, J. F. W.; Perry, D. H. Benzocyclobutenes, part 4. Synthesis of benzocyclobutene-1,2-diones by pyrolytic methods. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1834–1840.
9. Al'-Assar, F.; Zelenin, K. N.; Lesiovskaya, E. E.; Bezhan, I. P.; Chakchir, B. A. Synthesis and pharmacological activity of 1-hydroxy-, 1-amino-, and 1-hydrazino-substituted 2,3-dihydro-1H-pyrazolo[1,2-a]pyridazine-5,8-diones and 2,3-dihydro-1H-pyrazolo[1,2-b] phthalazine-5,10-diones. *Pharm. Chem. J.* **2002**, *36*, 598–603.
10. Jain, R. P.; Vederas, J. C. Structural variations in keto-glutamines for improved inhibition against hepatitis A virus 3C proteinase. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3655–3658.

11. Carling, R. W.; Moore, K. W.; Street, L. J.; Wild, D.; Isted, C.; Leeson, P. D.; Thomas, S.; O'Connor, D.; McKernan, R. M.; Quirk, K.; Cook, S. M.; Atack, J. R.; Wafford, K. A.; Thompson, S. A.; Dawson, G. R.; Ferris, P.; Castro, J. L. 3-Phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[3,4-a]phthalazines and analogues: High-affinity γ-aminobutyric acid-A benzodiazepine receptor ligands with α 2, α 3, and α 5-subtype binding selectivity over α 1. *J. Med. Chem.* **2004**, *47*, 1807–1822.
12. Kim, J. S.; Rhee, H.-K.; Park, H. J.; Lee, S. K.; Lee, C.-O.; Park Choo, H.-Y. Synthesis of 1-/2-substituted-[1,2,3]triazolo[4,5-g]phthalazine-4,9-diones and evaluation of their cytotoxicity and topoisomerase II inhibition. *Bioorg. Med. Chem.* **2008**, *16*, 4545–4550.
13. Ghahremanzadeh, R.; Shakibaei, G. I.; Bazgir, A. One-pot synthesis of 1H-pyrazolo [1,2-b]phthalazine-5,10-dione derivatives. *Synlett* **2008**, 1129–1132.
14. Grasso, S.; De Sarro, G.; De Sarro, A.; Micale, N.; Zappala, M.; Puja, G.; Baraldi, M.; De Micheli, C. Synthesis and anticonvulsant activity of novel and potent 6,7-methylenedioxyphthalazin-1(2H)-ones. *J. Med. Chem.* **2000**, *43*, 2851–2859.
15. Amarasekara, A. S.; Chandrasekara, S. Reaction of 1,4-phthalazinedione with furfural: Formation of the [5,6]benza-3a,7a-diazaindane system via an unusual skeletal rearrangement. *Org. Lett.* **2002**, *4*, 773–775.
16. Schröder, J.; Henke, A.; Wenzel, H.; Brandstetter, H.; Stammler, H. G.; Stammler, A.; Pfeiffer, W. D.; Tschesche, H. Structure-based design and synthesis of potent matrix metalloproteinase inhibitors derived from a 6H-1,3,4-thiadiazine scaffold. *J. Med. Chem.* **2001**, *44*, 3231–3243.
17. Sugawara, H.; Endoh, M. (−)-Enantiomer EMD 57439 antagonizes the Ca^{2+} sensitizing effect of (+)-enantiomer EMD 57033 on diastolic function but not on systolic function in rabbit ventricular cardiomyocytes. *Jpn. J. Pharmacol.* **1999**, *80*, 55–65.
18. Himmel, H. M.; Amos, G. J.; Wettwer, E.; Ravens, U. Effects of the calcium sensitizer [+]-EMD 60263 and its enantiomer [−]-EMD 60264 on cardiac ionic currents of guinea pig and rat ventricular myocytes. *J. Cardiovasc. Pharmacol.* **1999**, *33*, 301–308.
19. (a) Eggenweiler, H. M.; Wolf, M. Combination of a pde iv inhibitor and a tnf-α antagonist. Ger. Patent 10,150,517. *Chem. Abstr.* **2003**, *138*, 297702; (b) Warner, J. M. PCT Int. Appl. WO 2,004,067,006. *Chem. Abstr.* **2004**, *141*, 185092.
20. Rüfenacht, K. Arbeiten über phosphorsäure- und thiophosphorsäureester mit einem heterocyclischen Substituenten, 7: Mitteilung. thio- und dithiophosphorsäureester von der art des GS 13005 mit einem analogen oder homologen heterocyclischen ring. *Helv. Chim. Acta* **1973**, *56*, 2186–2204.
21. Suzuki, T.; Kimura, K.; Watanabe, R. Production of triazole-based compound. Jpn. Kokai 2,000,143,664. *Chem. Abstr.* **2000**, *132*, 347594.
22. Guravaiah, N.; Rajeswar Rao, V. Stereoselective synthesis of substituted 2-(Z-styrylsulfonyl)-1H-imidazoles and benzothiazole. *Synth. Commun.* **2010**, *40*, 808–813.
23. Srinivas, V.; Rajeswar Rao, V. One-pot synthesis of 2-amino-5,10-dihydro-5,10-dioxo-4-phenyl-4H-benzo[*g*]chromene derivatives catalyzed by $ZnCl_2$. *Synth. Commun.* **2011**, *41*, 806–811.
24. Chunduru, V. S. R.; Rajeswar Rao, V. Synthesis of coumarin-substituted thiazolyl-pyrazolone derivatives via one-pot reaction. *J. Sulfur Chem.* **2010**, *31*, 545–550.
25. Rajeswar Rao, V.; Padmanabha Rao, T. V. Studies of thiazolyl, imidazolyl-2H-1-benzopyran-2-ones. *Indian J. Chem.* **1986**, *25B*, 413–415.