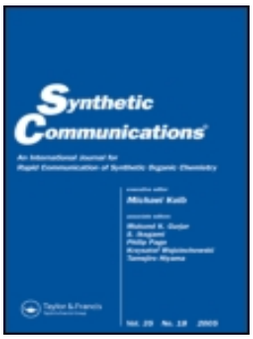

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Novel One-Pot Multicomponent Synthesis of Substituted 2,3-Dihydro-2-(6-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)phthalazine-1,4-diones and Substituted 3-[3-(N'-Benzylidene-hydrazino)-7H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazin-6-yl]-4-hydroxy-6-methyl-pyran-2-ones

Bade Thirupaiah & Rajeswar Rao Vedula

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NOVEL ONE-POT MULTICOMPONENT SYNTHESIS OF SUBSTITUTED 2,3-DIHYDRO-2-(6-(4-HYDROXY-6-METHYL-2-OXO-2H-PYRAN-3-YL)-7H-[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZIN-3-YL)PHTHALAZINE-1,4-DIONES AND SUBSTITUTED 3-[3-(N′-BENZYLIDENE-HYDRAZINO)-7H-[1,2,4] TRIAZOLO[3,4-b][1,3,4]THIADIAZIN-6-YL]-4-HYDROXY-6-METHYL-PYRAN-2-ONES

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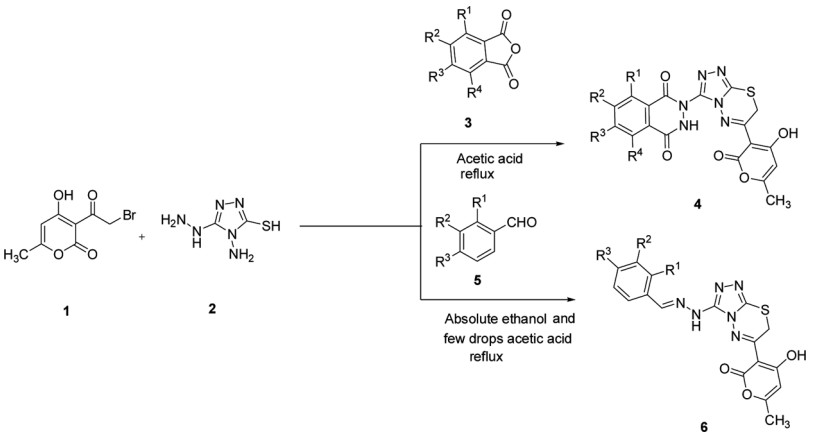
GRAPHICAL ABSTRACT



Abstract *A one-pot procedure has been developed for the synthesis of substituted 2,3-dihydro-2-(6-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-7H-[1,2,4]triazolo[3,4-b] [1,3,4]-thiadiazin-3-yl)phthalazine-1,4-diones by reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one, 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol, and phthalic anhydrides in acetic acid medium. Similarly, a one-pot, three-component synthetic procedure has been developed for substituted 3-[3-(N[1]-benzylidene-hydrazino)-7H-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazin-6-yl]-4-hydroxy-6-methyl-pyran-2-ones from 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one, 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol, and various aromatic aldehydes in absolute ethanol and a few drops of glacial acetic acid.*

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[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords 4-Amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol; 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one; 2,3-dihydrophthalazine-1,4-dione; Schiff base; triazolothiadiazine

INTRODUCTION

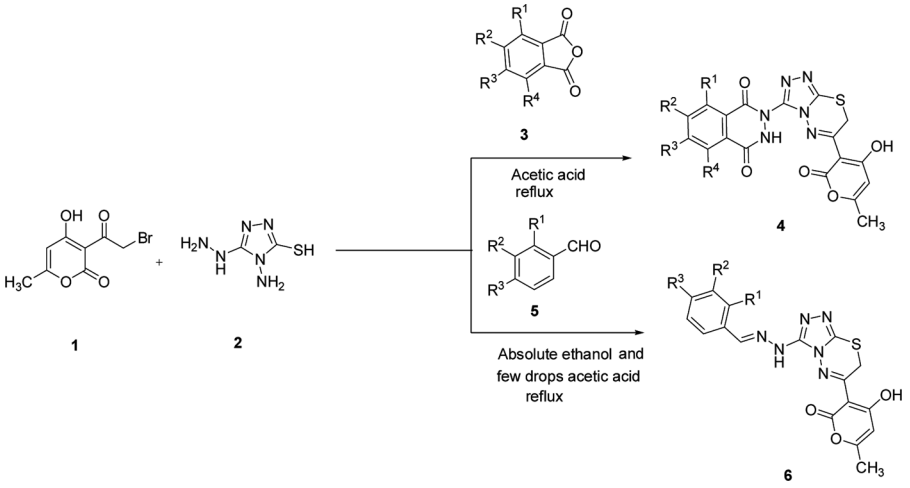
Multicomponent reactions have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[1] Multicomponent reactions are well known to be selective, efficient, atom-economical, time-saving, and easy to perform while requiring readily available starting materials.[2] The [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines possess antimicrobial activities.[3] The [1,2,4]triazolo[3,4-b][1,3,4]thiadiazine system is reported to possess significant antibacterial, antifungal, herbicidal, and anthelmintic activities.[4,5] [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazine[6] is reported to show a broad spectrum of pharmacological properties such as antitubercular,[7] diuretics,[8] and hypoglycaemic[9] activities. 3,6-Disubstituted-7H-s-trizolo[3,4-b][1,3,4]thiadiazine derivatives were prepared by condensing 4-amino-5-mecapto-3-alkyl/aryl-1,2,4-triazoles with substituted α-halocarbonyl compounds.[10,11] Phthalazine has played a unique role in the design and synthesis of novel biologically active compounds, serving as anticonvulsant,[12] vasorelaxant,[13] anti-HIV,[14] PDE3/PDE4 inhibitory agents,[15] antiasthamatic,[16] leishmanicidal,[17] and antidiabetic.[18] We designed the synthesis of novel substituted 1,2,4-triazolothiadiazine derivatives starting from bromodehydroacetic acid and 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol.

RESULTS AND DISCUSSION

4-Amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol (parpald) is a substrate for the synthesis of diverse N,S-heterocycles by multicomponent reactions (MCRs). Most interestingly, the outcomes of the final products from the MCRs involving 4-amino-5--hydrazino-4H-[1,2,4]triazole-3-thiol are substrated dependent. Therefore, a one-pot, three-component synthesis of triazolo thiadiazin-3-yl phthalazine1,4-dione was performed with excellent yields. In this method, thiadiazine and 2,3-dihydrophthalazine-1,4-dione rings were formed in one pot. Reaction of an equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one, 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol, and phthalic anhydride in acetic acid gave the final products of 2,3-dihydro-2-(6-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-7H-[1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazin-3-yl)phthalazine-1,4-dione derivatives **4a** and **b** (Scheme 1).

Similarly, reaction of an equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one, 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol, and various aromatic aldehydes in absolute ethanol and few drops of glacial acetic acid gave the final products of 3-[3-(N^1-benzylidene-hydrazino)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl]-4-hydroxy-6-methyl-pyran-2-one derivatives **6** (Scheme 2). The reaction time along with the yields of the products are given in Table 1.

A plausible mechanism for the formation of products **4** and **6** is proposed in Scheme 2. In the first step, elimination of HBr from **1** and **2** will give an intermediate



Scheme 1. Synthetic approach to compounds **4** and **6**.

oxonium ion **A**. The nitrogen of NH_2 of the ring attacks on the protonated corbonyl carbon followed by loss of water molecule to give the intermediate **C**. This undergoes cyclocondensation with phthalic anhydride to give an end product. Then **C** reacts with carbocation of araldehyde to give an intermediate **F**. On loss of water molecule and loss of proton, this gives the title products **6**.

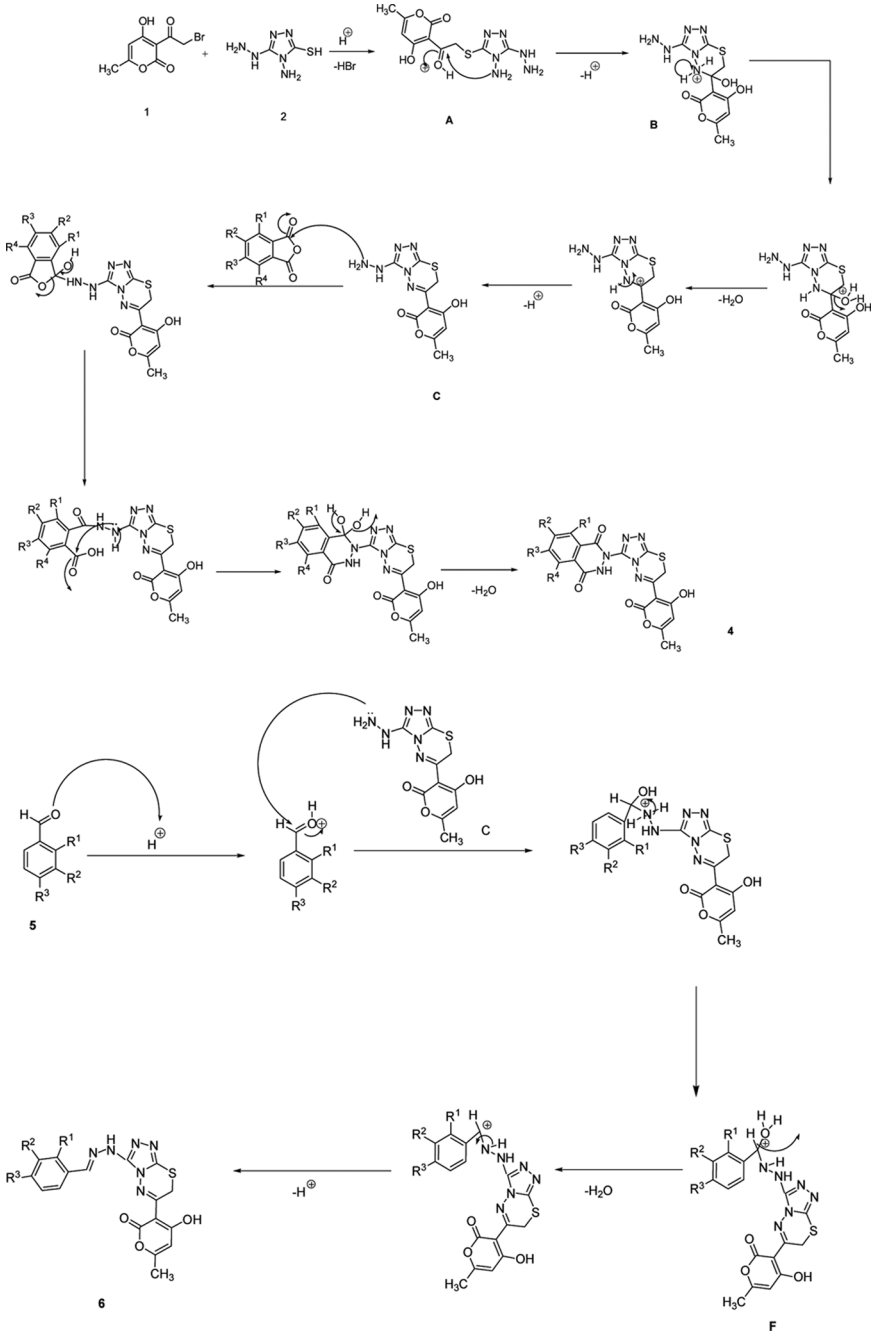
All the structures of newly synthesized compounds have been confirmed by their spectral data. The infrared (IR) spectrum of compound **4a** showed prominent peaks at 1720 cm^{-1} for –C=O of lactone, 1641 cm^{-1} for –C=O of amide, 3260 cm^{-1} for –NH, and 3434 cm^{-1} for –OH, whereas the ^{1}H NMR spectrum of compound **4a** showed characteristic singlets for CH_3 of pyran at δ 2.31, CH_2 of thiadiazine at δ 4.47, CH of pyran at δ 6.15, NH at δ 10.30, and OH at δ 12.84 ppm. Similarly, the IR spectrum of compound **6a** showed prominent peaks at 1738 cm^{-1} for –C=O of lactone, 3230 cm^{-1} for –NH, and 3435 cm^{-1} for –OH. The ^{1}H NMR spectrum of compound **6a** showed charecteristic singlets for CH_3 of pyran at δ 2.22, Ar-OCH_3 at δ 3.86, CH_2 of thiadiazine at δ 4.48, CH of pyran at δ 6.15, Ar-CH=N at δ 8.25, NH at δ 10.77, and OH at δ 12.90 ppm. All these spectral data clearly confirm the formation of products **4a** and **b** and **6a–j**.

CONCLUSION

In conclusion, we have developed a facile and efficient one-pot, three-component protocol for the synthesis of novel substituted [1,2,4]triazolo-[3,4-b][1,3,4]thiadiazin derivatives. This reaction proceeded smoothly in good to excellent yields. In all cases, the products can be purified by simple recrystallization.

EXPERIMENTAL

All the chemicals used in this work were purchased from commercial sources. Melting points were determined with an Electrothermal-9100 apparatus.



Scheme 2. Reaction mechanism of final compounds **4** and **6**.

The purity of the compounds was checked by thin-layer chromatography (TLC) plates (E. Merck Mumbai, India). IR spectra (KBr) were recorded on a Perkin-Elmer 100 S spectrometer. ^{1}H NMR spectra were recorded on a Bruker WM-400

Table 1. Synthesis of final products (**4** and **6**)

Entry	R^1	R^2	R^3	R^4	Product	Time (h)	Yield (%)
1	H	H	H	H	**4a**	8	75
2	Br	Br	Br	Br	**4b**	9	80
3	H	H	OCH_3	—	**6a**	9	75
4	H	H	Br	—	**6b**	8	80
5	H	H	Cl	—	**6c**	9	78
6	H	H	$N(CH_3)_2$	—	**6d**	8	75
7	H	OCH_3	OCH_3	—	**6e**	8	85
8	H	NO_2	H	—	**6f**	9	75
9	H	OCH_3	OH	—	**6g**	9	70
10	OH	H	OH	—	**6h**	9	65
11	H	H	OH	—	**6i**	9	75
12	OH	H	H	—	**6j**	9	70

spectrometer in δ ppm using tetramethylsilane (TMS) as the standard. ^1H and ^{13}C NMR spectra were obtained in dimethylsulfoxide (DMSO) using TMS as reference standard (δ in parts per million, J in hertz). Electron ionization mass spectra (EI-MS) were determined on a Perkin-Elmer instrument (SCIEX API-2000, ESI) at 12.5 eV.

General Procedure for the One-Pot Synthesis of 2,3-Dihydro-2-(6-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-7H-[1,2,4]-triazolo [3,4-b][1,3,4]thiadiazin-3-yl)phthalazine-1,4-dione (4a)

An equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one (1.0 mmol), 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol (1.0 mmol), and phthalic anhydride (1.0 mmol) was taken in glacial acetic acid. The reaction mixture was heated at 80 °C for about 8 h and cooled to room temperature. The solid obtained was filtered, washed with water, and recrystallized from ethanol. Light yellow solid (0.318 g, 75%); mp 209–211 °C; IR (KBr) (υ_{max}/cm^{-1}): 3434, 3260, 1720, 1641; ^1H NMR (400 MHz, DMSO-d_6) 2.31 (s, 3H, CH_3), 4.47 (s, 2H, CH_2), 6.15 (s, 1H, CH), 7.62 (d, 2H, $J = 7.2$ Hz, ArH), 7.78 (d, 2H, $J = 7.6$ Hz, ArH), 10.30 (s, 1H, NH), 12.84 (s, 1H, OH). ^{13}C NMR (400 MHz, DMSO-d_6) 22.1, 25.3, 99.3, 102.0, 121.2, 127.9, 128.7, 133.5, 136.1, 142.5, 149.4, 161.0, 164.4, 174.5. Mass spectrum m/z: 425 (M + H). Anal. calcd. for $C_{18}H_{12}N_6O_5S$: C, 50.94; H, 2.85; N, 19.80; Found: C, 50.90; H, 2.80; N, 19.75.

General Procedure for the One-Pot Synthesis of 4-Hydroxy-3-{3-[N^1-(4-methoxy-benzylidene)-hydrazino]-7H-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazin-6-yl}-6-methyl Pyran-2-one (6a)

Equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one (1.0 mmol), 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol (1.0 mmol), and 4-methoxybenzaldehyde (1.0 mmol) was taken in absolute ethanol containing a catalytic amount of acetic acid. The reaction mixture was heated at 60–65 °C for about 9 h and cooled to room temperature. The solid obtained was filtered, washed

with water, and recrystallized from ethanol. Yellow solid (0.309 g, 75%); mp 204–206 °C; IR (KBr) (υ_{max}/cm^{-1}): 3435, 3230, 1738; ^{1}H NMR (400 MHz, DMSO-d_6) 2.22 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.48 (s, 2H, CH_2), 6.12 (s, 1H, CH), 6.97 (d, 2H, $J = 8.4$ Hz, ArH), 7.55 (d, 2H, $J = 8.8$ Hz, ArH), 8.25 (s, 1H, CH), 10.46 (s, 1H, NH), 12.90 (s, 1H, OH). ^{13}C NMR (400 MHz, DMSO-d_6) 22.2, 24.9, 55.2, 108.7, 114.2, 114.4, 124.9, 127.3, 127.8, 130.8, 144.0, 149.6, 153.3, 160.1, 164.3, 174.9. Mass spectrum m/z: 411 (M-H). Anal. calcd. for $C_{18}H_{16}N_6O_4S$: C, 52.42; H, 3.91; N, 20.38. Found: C, 52.36; H, 3.96; N, 20.34.

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REFERENCES

1. (a) Tietze, L. F.; Modi, A. Multicomponent domino reactions for the synthesis of biologically active natural products and drugs. *Med. Res. Rev.* **2000**, *20*, 304–322; (b) Ugi, I.; Dömling, A.; Werner, B. Since 1995 the new chemistry of multicomponent reactions and their libraries, including their heterocyclic chemistry. *J. Heterocyclic. Chem.* **2000**, *37*, 647–658; (c) Orru, R. V. A.; de Greef, M. Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis* **2003**, *10*, 1471–1499.
2. Wender, P. A.; Miller, B. L. Synthesis at the molecular frontier. *Nature* **2009**, *460*, 197–201.
3. Demirbas, N.; Demirbas, A.; Karaoglu, S. A.; Çelik, E. Synthesis and antimicrobial activities of some new [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles and [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines. *Arkivoc* **2005**, *1*, 75–91.
4. Holla, B. S.; Udupa, K. V. Synthesis, spectral studies, and biological activities of some N-bridged heterocycles derived from 3-arylaminomethyl-4-amino-5-mercapto-1,2,4-triazoles. *Farmaco* **1992**, *47*, 305–318.
5. Molina, P.; Alajarin, M.; Perezdevega, M. J.; Foces-Foces, Cano, F. H.; Claramunt, R.; Elguero, J. Synthesis of 6,7-dihydro-5H-1,2,4-triazolo(3,4-b)-1,3,4-thiadiazines. *J. Chem. Soc. Perkin Trans. 1* **1987**, *18*, 1853–1860.
6. Lawson, A.; Tinkler, R. B. Chemistry of thiadiazole and thiadiazine S-oxides. *Chem. Rev.* **1970**, *70*, 593–618.
7. Mir, I.; Siddiqui, M. T.; Comrie, A. Antituberculosis agents—I: α-[5-(2-Furyl)-1,2,4-triazol-3-ylthio] acethydrazide and related compounds. *Tetrahedron* **1970**, *26*, 5235–5238.
8. Hester, J. B.; Ludens, J. H.; Emmert, D. E.; West, B. E. 1-(2-Aminoethyl)-6-aryl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepines with diuretic and natriuretic activity. *J. Med. Chem.* **1989**, *32*, 1157–1163.
9. Holla, B. S.; Veerndra, B.; Shivananda, M. K.; Poojary, B. Synthesis characterization and anticancer activity studies on some mannich bases derived from 1,2,4-triazoles. *Eur. J. Med. Chem.* **2003**, *38*, 759–767.
10. EI-Dawy, M. A.; Omar Amohsen, M. E.; Ismail, A. M.; Hazaa, A. A. B. Potential broad-spectrum anthelmintics, IV: Design, synthesis, and antiparasitic screening of certain 3,6-disubstituted-(7*H*)-*s*-triazolo-[3,4-*b*][1,3,4]thiadiazine derivatives. *J. Pharm. Sci.* **1983**, *72*, 45–50.

11. Rajeswar Rao, V.; Ravi Kumar, V.; Aditya Vardhan, V. A facile one-step synthesis of [3-(2-hydrazine-4-thiazolyl)coumarino] dimethyl methines and some 3-substituted-7H-6-(6/8,6,8-substituted-3-coumarino)-s-triazolo[3,4-b][1,3,4]thiadiazines. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *152*, 257–264.
12. Zhang, L.; Guan, L.; Sun, X.; Wei, C.; Chai, K.; Quan, Z. Synthesis and anticonvulsant Activity of 6-alkoxy-[1,2,4]triazolo[3,4-a]phthalazines. *Chem. Biol. Drug. Des.* **2009**, *73*, 313–319.
13. Deshpande, S. R.; Ghongade, A. M.; Pai, V. K. Synthesis and biological evaluation of 2-(N-substituted)-3H-phthalazin-1,4-diones and 1-(N-substituted) 2,4,5-trihydropyridazin-3,6-diones as potent vasodilators. *Indian J. Pharm. Ed. Res.* **2010**, *44*(1), 1–7.
14. Bedoya, L. M.; Olmo, E.; Sancho, R.; Barboza, B.; Beltrán, M.; García-Cadenas, A. E.; Sánchez-Palomino, S.; López-Pérez, J. L.; Muñoz, E.; Feliciano, A. S.; Alcamí, J. Anti-HIV activity of stilbene-related heterocyclic compounds. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4075–4079.
15. Mey, M. V.; Bommeleâ, K. M.; Boss, H.; Hatzelmann, A.; Slingerland, M. V.; Sterk, G. J.; Timmerman, H. Synthesis and structure-activity relationships of cis-tetrahydrophthalazinone/pyridazinone hybrids: A novel series of potent dual PDE3/PDE4 inhibitory agents. *J. Med. Chem.* **2003**, *46*, 2008–2016.
16. Yamaguchi, M.; Koga, T.; Kamei, K.; Akima, M.; Maruyama, N.; Kuroki, T.; Hamana, M.; Ohi, N. Novel antiasthmatic agents with dual activities of thromboxane A_2 synthetase inhibition and bronchodilation, IV: 2-[2-(1-imidazolyl)ethy1]-4-(3-pyridyl)-1(2H)-phthalazinones. *Chem. Pharm. Bull.* **1994**, *42*(9), 1850–1853.
17. Olmo, E.; Armas, M. G.; López-Pérez, J. L.; Muñoz, V.; Deharo, E.; Feliciano, A. S. Leishmanicidal activity of some stilbenoids and related heterocyclic compounds. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2123–2126.
18. Madhavan, G. R.; Chakrabarti, R.; Kumar, S. K. B.; Misra, P.; Mamidi, R. N. V. S.; Balraju, V.; Kasiram, K.; Babu, R. K.; Suresh, J.; Lohray, B. B.; Lohray, V. B.; Iqbal, J.; Rajagopalan, R. Novel phthalazinone and benzoxazinone-containing thiazolidinediones as antidiabetic and hypolipidemic agents. *Eur. J. Med. Chem.* **2001**, *36*, 627–637.