Med Chem Res (2007) 16:392–401
DOI 10.1007/s00044-007-9051-6

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological evaluation of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles

M. Gopalakrishnan · J. Thanusu · V. Kanagarajan

Received: 4 August 2007 / Accepted: 5 November 2007 / Published online: 11 December 2007

Abstract New 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles **23–27** are synthesized, characterized by melting point, elemental analysis, magnetic spectroscopy (MS), Fourier-transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (NMR) (^{1}H and ^{13}C) spectra and evaluated for their in vitro antibacterial and antifungal activities. Compounds **23–27** are more potent against Gram-positive bacterial strains, namely *Staphylococcus aureus* and *β-Haemolytic streptococcus*. However compounds **23–27** possess potent activity against *Klebsiella pneumonia*, a Gram-negative bacterial strain, compared to the standard drug used, ciprofloxacin. In general, all the synthesized compounds exert a wide range of modest in vitro antifungal activity against *Rhizopus* and *Microsporum gypsuem* than the standard drug, fluconazole.

Keywords 3,3-dimethyl-2,6-diarylpiperidin-4-one · 1,2,3-thiadiazoles · Thionyl chloride · Antibacterial activity · Antifungal activity

Introduction

It is well known that a number of heterocyclic compounds containing sulfur possess different pharmacophoric properties (Shafiee *et al.*, 1973; Katritzky, 1985; Balasankar *et al.*, 2007) 1,2,3-Thiadiazoles are useful intermediates in organic synthesis (Rovira, 1994), as well as being an important of class of biologically

M. Gopalakrishnan (✉) · J. Thanusu · V. Kanagarajan
Synthetic Organic Chemistry Laboratory, Department of Chemistry, Annamalai University, Annamalainagar 608 002, Tamil Nadu, India
e-mail: profmgk@yahoo.co.in

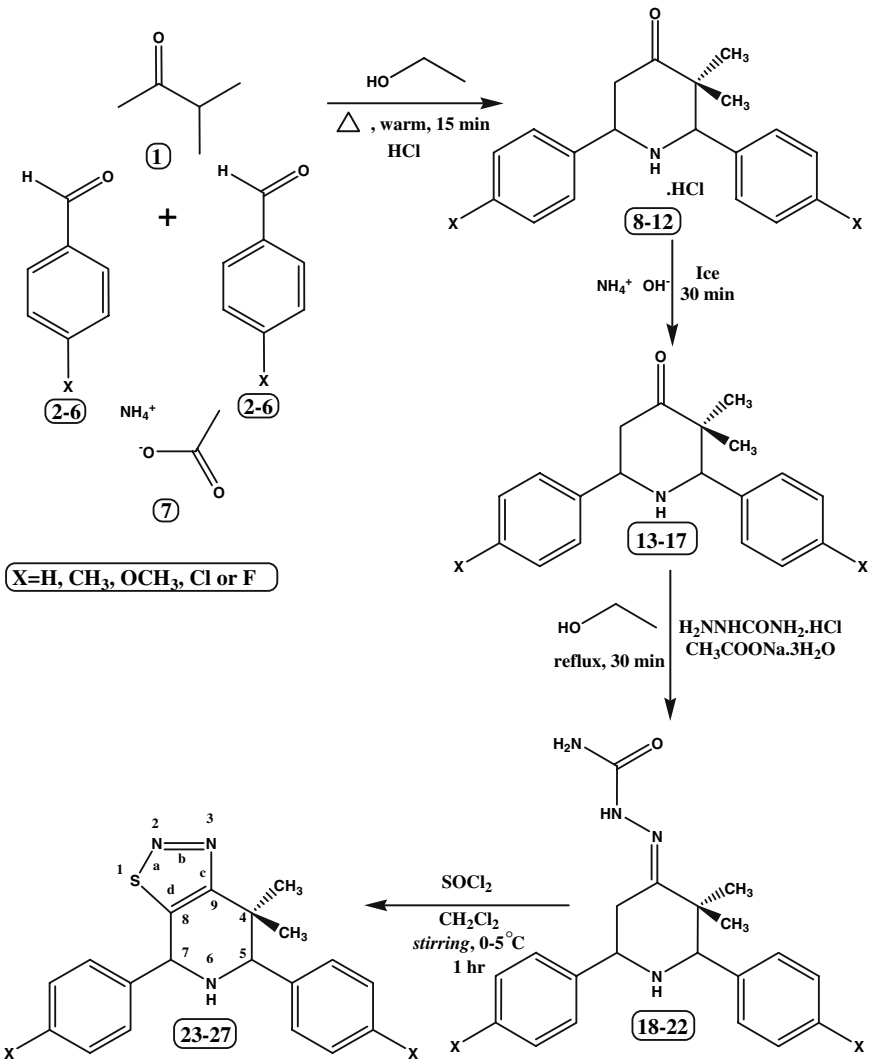
active compounds (Stanetty *et al.*, 1998; Britton *et al.*, 1984; Stanetty *et al.*, 1996; Lewis *et al.*, 1979). For instance, 4,5-bis(4'-methoxyphenyl)-1,2,3-thiadiazoles has been found to be an active inhibitor of collagen-induced platelet aggregation in vitro (Thomas *et al.*, 1985). Originally, 1,2,3-thiadiazoles were synthesized from the reaction of α-methylene (or ethyl) hydrazones (Hurd *et al.*, 1955). Many other methods have since been developed for the synthesis of 1,2,3-thiadiazoles (Thomas *et al.*, 1984; Fujita *et al.*, 1993), of which the Hurd–Mori cyclization (Byron *et al.*, 1966; Tumkevicius *et al.*, 2003; Ghandi *et al.*, 2000; Smeets *et al.*, 1998) of α-methylene ketones offers the most convenient methodology.

Piperidin-4-one nuclei have aroused great interest, both in the past and in recent years, due to their wide variety of biological properties, such as being antiviral, antitumor (El-Subbagh *et al.*, 2000; Watson *et al.*, 2001), having central nervous system effects (Ganellin *et al.*, 1965), local anesthetic properties (Hagenbach *et al.*, 1952), and anticancer (Ileana *et al.*, 1989) and antimicrobial activity (Mokio *et al.*, 1989). Their derivative, piperidine, is also biologically important and act as a neurokinin receptor antagonist (Dimmock *et al.*, 1997), an analgesic and an anti-hypertensive (Kubota *et al.*, 1998).

In recent years there has been a great deal of interest in exploiting multiple proximal functional groups in the design of novel structures capable of performing a variety of functions. One such functional addition is the α-keto methylene group, which has been used as a building block for 1,2,3-thiadiazoles. These observations place new emphasis on the synthesis of 2,6-diarylpiperidin-4-one derivatives with a view to incorporation of a bioactive heterocyclic nucleus, such as 1,2,3-thiadiazoles, intact, for the evaluation of associated antibacterial and antifungal activity. Synthesis of molecules that are novel but still resemble known biologically active molecules by virtue of the presence of some critical structural features is an essential component of the search for new leads in drug design. In continuation of our earlier work on 3-alkyl-2,6-diarylpiperidin-4-one derivatives (Gopalakrishnan *et al.*, 2007; Gopalakrishnan *et al.*, 2007), and 1,2,3-thiadiazoles (Balasankar *et al.*, 2005)**,** we report the synthesis of 3,3-dimethyl-2,6-diarylpiperidin-4-ones that posses an α-keto methylene group, thus permitting the preparation of a new class of compounds, 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles.

Chemistry

The only available method for synthesis of the target molecule is the conversion of semicarbazones of the respective 3,3-dimethyl-2,6-diarylpiperidin-4-ones by thionyl chloride in dichloromethane. The schematic representation and analytical data for the synthesized compounds **23–27** are furnished Scheme 1 and Table 1, respectively. A four-step synthetic strategy yields compounds **23–27**. A mixture of 3-methyl-butan-2-one (**1**), the appropriate benzaldehyde (**2–6**)**,** and ammonium acetate (**7**) in the ratio of 1:2:1, is warmed for 15 minutes and hydrochloric acid is then added to afford 3,3,-dimethyl-2,6-diaryl-piperidin-4-ones hydrochloride **8–**



Scheme. 1 Synthetic pathway for the synthesis of novel bioactive 5,7-Diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles

12, which upon neutralization with aqueous ammonia at 0°C give the respective 3,3,-dimethyl-2,6-diaryl-piperidin-4-ones **13–17**. Piperidones are converted into their semicarbazones **18–22** and are eventually cyclized into 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles **23–27** using thionyl chloride in dichloromethane. The structures of the compounds are elucidated by melting points, elemental analysis, MS, FT-IR, NMR (^{1}H and ^{13}C) spectroscopic data.

Table 1 Analytical data of compounds 23–27

Compound	X	Yield (%)	m.p. (°C)	Elemental analysis (%)			Molecular formula *m/z* (M^+)
				C Found (calculated)	H Found (calculated)	N Found (calculated)	
23	H	45	127–28	70.95 (70.99)	5.91 (5.96)	13.04 (13.07)	(322) $C_{19}H_{19}N_3S$
24	CH_3	51	143–45	72.15 (72.17)	6.59 (6.63)	11.99 (12.02)	(350) $C_{21}H_{23}N_3S$
25	OCH_3	55	149–51	66.08 (66.12)	6.05 (6.08)	10.98 (11.01)	(382) $C_{21}H_{23}N_3O_2S$
26	Cl	62	161–63	58.44 (58.46)	4.36 (4.39)	10.73 (10.77)	(391) $C_{19}H_{17}Cl_2N_3S$
27	F	60	165–66	63.82 (63.85)	4.75 (4.79)	11.74 (11.76)	(358) $C_{19}H_{17}F_2N_3S$

Results and discussion

Biological evaluation

Antibacterial activity

All of the newly synthesized novel target molecule 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles **23–27** were tested for their antibacterial activity in vitro (Table 2) against *Staphylococcus aureus, β-Haemolytic streptococcus, Vibreo cholerae, Salmonella typhii, Shigella felxneri, Escherichia coli, Klebsiella pneumonia*, and *Pseudomonas*. Ciprofloxacin, at a concentration of 5 μg/disc was used as standard drug for comparison, whose zone of inhibition values (mm) for *S. aureus, β-Haemolytic streptococcus, V. cholerae, S. typhii, S. felxneri, E. coli, K. pneumonia* and *Pseudomonas*, are 25, 28, 23, 22, 23, 24, 26, and 23 mm, respectively. In general, the synthesized novel 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles **23–27** exerted a wide range of modest antibacterial activity in vitro against Gram-positive bacterial strains, namely, *S. aureus* and *β-Haemolytic streptococcus* than the standard drug, ciprofloxacin. However, compounds **23–27** display potent activity against *K. pneumonia*, a Gram-negative bacterial strain.

Antifungal activity

The in vitro antifungal activity (Table 2) of the synthesized novel heterocyclic compounds **23–27,** was studied against the fungal strains viz., *Aspergillus flavus, Mucor, Rhizopus*, and *Microsporum gypsuem.* Fluconazole, at 100 units/disc concentration, was used as a standard drug whose zone of inhibition values (mm) for *A. flavus, Mucor, Rhizopus* and *M. gypsuem*, are 20 ±0.5 mm against all of the tested fungi. In general, the synthesized compounds exerted a wide range of modest in vitro antifungal activity against *Rhizopus* and *M. Gypsuem*, compared to the standard drug, fluconazole, but their activity decreased upon dilution.

Conclusion

In vitro antibacterial and antifungal activity profiles in differently substituted novel 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles **23–27** against the tested bacterial strains, viz., *S. aureus, β-Haemolytic streptococcus, V. cholerae, S. typhii, E. coli, K. pneumonia, Pseudomonas*, and the fungal strains, viz., *A. flavus, A. fumigatus, Mucor*, and *Rhizopus*, respectively, provide a useful structure–activity relationship correlate. This may be summarized as follows: the results of this study show that the presence of both electron-donating substituent (methyl, methoxy) and electron-withdrawing substituent (chloro, fluoro) at the *para* positions on the phenyl ring in compounds **23–27** are responsible for the activity against gram positive bacterial strains, namely, *S. aureus, β-Haemolytic*

Table 2 In vitro profile of compounds **23–27** against test bacteria and fungi

Micro organisms	Compound 23			Compound 24			Compound 25			Compound 26			Compound 27		
	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm
Staphylococcus aureus	−	++	+++	−	+++	++++	+	+++	++++	+	+++	++++	−	+++	++++
β-Haemolytic streptococcus	−	+	+++	−	++	++++	−	+	++++	−	+	++++	−	++	+++
Vibreo cholerae	+	+	++	+	++	++	+	++	++	+	+	+	+	++	++
Salmonella typhii	+	+	+	+	+	+	+	++	++	−	++	++	+	+	+
Shigella felxneri	−	+	++	+	++	++	+	++	++	+	+	+	+	++	++
Escherichia coli	−	+	+	−	+	++	−	++	++	−	+	++	−	++	++
Klebsiella pneumonia	+	++	+++	++	++	+++	−	++	+++	+	++	+++	++	++	+++
Pseudomonas	+	+	+	−	+	+	−	+	+	−	+	+	−	++	++
Aspergillus flavus	+	+	++	+	+	+	+	+	++	+	+	++	+	++	++
Mucor	−	+	++	−	++	++	+	++	++	−	+	+	−	++	++
Rhizopus	+	++	++	+	++	+++	−	+	+++	−	+	+++	+	+++	+++
Microsporum gypsuem	+	++	+++	++	+++	++++	+	++	++++	+	++	+++	++	+++	++++

(−) = inactive, (+) = weakly active (12−16 mm), (++) = moderately active (17–21 mm), (+++) = strong active (22–29 mm), (++++) = highly active (30–33 mm)

streptococcus. However, compounds **23–27** possess potent activity against *K. pneumonia*, a Gram-negative bacterial strain than the standard drug, ciprofloxacin. All the synthesized compounds **23–27** against *Rhizopus* and *M. gypsuem*, exert a wide range of modest in vitro antifungal activity, compared to the standard drug, fluconazole.

Experimental section

Microbiology

Materials

All of the bacterial strains, namely S. aureus, *β*-Haemolytic streptococcus, V. cholerae, S. typhii, S. felxneri, E. coli, K. pneumonia, Pseudomonas, and fungal strains, namely, A. flavus, Mucor, Rhizopus and M. gypsuem, were obtained from the Faculty of Medicine, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India.

In vitro antibacterial and antifungal activity

The in vitro activities of the compounds were tested in Sabourauds dextrose broth (SDB) (Hi-media, Mumbai) for fungi and nutrient broth (NB) (Hi-media, Mumbai) for bacteria by the disc diffusion method (Maruzella, 1958). The respective hydrochlorides of the test compounds **23–27** were dissolved in water to obtain 1 mg ml^{-1} stock solution and the different concentrations (100, 200, 500 ppm) are prepared from the stock solution. Seeded broth (containing microbial spores) was prepared in NB from 24 hour-old bacterial cultures grown on nutrient agar (Hi-media, Mumbai) at 37 ±1°C, while fungal spores from one- to seven-day-old Sabourauds agar (Hi-media, Mumbai) slant cultures were suspended in SDB. Sterile paper discs of 5 mm diameter were saturated with the three different concentrations and then placed in each of the seeded agar plates. The Petri dishes are incubated in a BOD incubator at 37°C for bacteria and 28°C for fungi. The zone of inhibition is recorded by visual observations after 24 hours for bacteria and after 72–96 hours for fungi. Moreover, the zone of inhibition is measured by excluding the diameter of the paper disc. Ciprofloxacin was used as the standard for bacteria and fluconazole as the standard for fungi, under analogous conditions. Ciprofloxacin, 5 μg/disc concentration, was used as the standard drug, whose zone of inhibition values (mm) for *S. aureus, β-Haemolytic streptococcus, V. cholerae, S. typhii, S. felxneri, E. coli, K. pneumonia* and *Pseudomonas* are 25, 28, 23, 22, 23, 24, 26, and 23 mm respectively. Fluconazole, at a concentration of 100 units/disc, was used as a standard drug whose zone of inhibition (mm) value for *A. flavus, Mucor, Rhizopus* and *M. gypsuem* is 20 ±0.5 mm.

Chemistry

Thin-layer chromatography (TLC) was used to assess the reactions and the purity of the products. All the reported melting points were taken in open capillaries and were uncorrected. Infrared (IR) spectra were recorded in KBr (pellet form) on a Nicolet-Avatar−330 FT-IR spectrophotometer and only noteworthy absorption values (cm^{-1}) are listed. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker AMX 400 NMR spectrometer using $CDCl_3$ as solvent. The electrospray ionization (ESI) positive MS spectra were recorded on a Bruker Daltonics liquid chromatography (LC) -MS spectrometer. Satisfactory microanalysis was obtained on a Carlo Erba 1106 CHN analyzer.

3,3-Dimethyl-2,6-diarylpiperidin-4-ones were prepared **8–17** by adopting the precedent set in the literature (Noller and Balaiah, 1948; Pandiarajan *et al.*, 1991).

*General method of preparation of 3,3-dimethyl-2,6-diarylpiperidin-4-one semicarbazones (**18–22**)*

A mixture of 3,3-dimethyl-2,6-diarylpiperidin-4-one (0.01 mol), semicarbazide hydrochloride (0.01 mol) and sodium acetate (0.02 mol) in ethanol (40 mL) was refluxed on a steam bath for 30 minutes and was then concentrated to one-third of its original volume. After cooling, the mixture was poured over crushed ice. The solid product thus obtained was then filtered off and recrystallized from ethanol twice to give 3,3-dimethyl-2,6-diarylpiperidin-4-one semicarbazones as crystalline solids.

*Typical procedure for the synthesis of 5,7-diphenyl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles (**23**)*

A solution of 3,3-dimethyl-2,6-diphenylpiperidin-4-one semicarbazone (**18**) (0.005 mol) in dichloromethane (50 mL) was treated with thionyl chloride (0.01 mol) and stirred for one hour at 0–5°C. The reaction mixture was decomposed with an ice-cold solution of sodium carbonate solution. The organic layer was washed with brine solution, then washed with excess of water and finally dried over anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, a gummy mass was obtained that solidified after treatment with petroleum ether (40–60). Final purification was done using column chromatography using silica gel (100–200 mesh), with dichloromethane-petroleum ether (40–60°C) (5 : 1) as eluent.

IR (KBr) (cm^{1}): 3304, 3061, 3030, 2967, 2922, 2881, 2796, 1583, 684, 764, 705; ^{1}H NMR (δ ppm): 1.24 (s, 3H, CH_3 at C-4), 1.69 (s, 3H, CH_3 at C-4), 1.93 (s, 1H, H_6); 4.79 (s, 1H, H_5), 5.37 (s, 1H, H_7), 7.20–7.58 (m, 10H, H_{arom}); ^{13}C NMR (δ ppm): 26.3 CH_3 at C-4, 28.0 CH_3 at C-4, 37.4 C-4, 69.3 C-5, 73.8 C-7, 126.7–128.6 –C_{arom} ,140.6, 142.7 *ipso*-C, 159.0 C-8, 170.6 C-9.

Compounds **24–27** were synthesized similarly.

*5,7-Bis(p-methylphenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles (**24**)*

IR (KBr) (cm^1): 3301, 3024, 2966, 2925, 2855, 1582, 817,675; ^{1}H NMR (δ ppm): 1.20 (s, 3H, CH_3 at C-4), 1.70 (s, 3H, CH_3 at C-4), 2.26 (s, 1H, H_6); 2.32 (s, 6H, CH_3 at Arom. ring), 4.84 (s, 1H, H_5), 5.40 (s, 1H, H_7), 7.14–7.25 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 21.0 CH_3 at Arom. ring, 26.7 CH_3 at C-4, 28.3 CH_3 at C-4, 37.7 C-4, 68.3 C-5, 73.4 C-7, 127.2–142.4 –C_{arom} , 158.4 C-8, 170.1 C-9.

*5,7-Bis(p-methoxylphenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles (**25**)*

IR (KBr) (cm^{-1}):3313, 2957, 2924, 2921, 1576, 834, 678; ^{1}H NMR (δ ppm): 1.37 (s, 3H, CH_3 at C-4), 1.53 (s, 3H, CH_3 at C-4), 2.34 (s, 1H, H_6); 3.82 (s, 6H, OCH_3 at Arom. ring), 4.78 (s, 1H, H_5), 5.35 (s, 1H, H_7), 7.21–7.41 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 24.4 CH_3 at C-4, 25.4 CH_3 at C-4, 37.6 C-4, 55.1, 55.4 -OCH_3 at Arom. ring, 68.1 C-5, 73.3 C-7, 113.7–131.8, 159.3, 159.6 –C_{arom} ,158.4 C-8, 170.3 C-9.

*5,7-Bis(p-chlorophenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles (**26**)*

IR (KBr) (cm^{-1}): 3325, 3291, 2928, 2861, 1578, 834, 686; ^{1}H NMR (δ ppm): 1.21 (s, 3H, CH_3 at C-4), 1.70 (s, 3H, CH_3 at C-4), 2.14 (s, 1H, H_6), 4.47 (s, 1H, H_5), 5.08 (s, 1H, H_7), 7.18–7.47 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 26.2 CH_3 at C-4, 28.3 CH_3 at C-4, 37.3 C-4, 68.7 C-5, 73.0 C-7, 128.0–138.7 –C_{arom} , 158.5 C-8, 170.7 C-9.

*5,7-Bis(p-fluorophenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles (**27**)*

IR (KBr) (cm^1): 3318, 3297, 2924, 2857, 1574, 1211, 825, 681; ^{1}H NMR (δ ppm): 1.22 (s, 3H, CH_3 at C-4), 1.76 (s, 3H, CH_3 at C-4), 2.18 (s, 1H, H_6), 4.55 (s, 1H, H_5), 5.08 (s, 1H, H_7), 7.26–7.47 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 26.6 CH_3 at C-4, 28.5 CH_3 at C-4, 37.7 C-4, 69.0 C-5, 73.4 C-7, 128.5–139.4 –C_{arom} , 159.1 C-8, 171.5 C-9.

References

Balasankar T, Gopalakrishnan M, Nagarajan S (2007) Synthesis and anti-bacterial activity of some 5-(4-biphenyl)-7-aryl[3,4-d]-1,2,3-benzoselenadiazoles. J Enz Inhib Med Chem 22:171

Balasankar T, Gopalakrishnan M, Nagarajan S (2005) Synthesis and antibacterial activity of some 5-(4-biphenylyl)-7-aryl[3,4-d][1,2,3]-benzothiadiazoles. Eur J Med Chem 40:728

Britton TC, Lobl TJ, Chidester CG (1984) Novel 1,2,3-thiadiazolyl sulfines from the reaction of N-substituted hydrazones with thionyl chloride. J Org Chem 49:4773

Byron DJ, Gray GW, Wilson RCJ (1966) The synthesis of some substituted biphenyl-4-carboxylic acids, 4-biphenylacetic acids and 4-amino biphenyls. J Chem Soc (C) 13:840

Dimmock JR, Kumar P (1997) Anticancer and cytotoxic properties of Mannich bases. Curr Med Chem 4:1

El-Subbagh HI, Abu-Zaid SM, Mahran MA, Badria FA, Alofaid AM (2000) Synthesis and biological evaluation of certain α, β-unsaturated ketones and their corresponding fused pyridines as antiviral and cytotoxic agents. J Med Chem 43:2915

Fujita M, Kobari T, Hiyama T, Konda K (1993) On the regioselectivity in the Hurd-Mori reaction. Heterocycles 36:33

Ganellin CR, Spickett RG (1965) Compounds affecting the central nervous system. 1,4-piperidones and related compounds. J Med Chem 8:619

Ghandi H, Anfoka C (2000) Benzo-(1,2,3)-thiadiazole-7-carbothioic acid-S-methyl esters induces systematic resistance in tomato to cucumber mosaic virus. Crop Prot 19:401

Gopalakrishnan M, Sureshkumar P, Thanusu J, Kanagarajan V, Govindaraju R, Jayasri G (2007) A convenient 'one-pot' synthesis and in vitro microbiological evaluation of novel 2,7-diaryl-[1,4]-diazepan-5-ones. J Enzyme Inhib Med Chem (in press)

Gopalakrishnan M, Sureshkumar P, Thanusu J, Prabhu C, Kanagarajan V (2007) One-pot conversion of piperidine-4-ones to [1,4]-diazepan-5-ones under microwave irradiation using silica gel supported $NaHSO_4$ catalyst. J Chem Res 2:80

Hagenbach RE, Gysin H (1952) Piperidones as potential antitumour agents. Experimentia 8:184

Hurd CD, Mori RI (1955) On acylhydrazones and 1,2,3-thiadiazoles. J Am Chem Soc 77:5359

Ileana B, Dobre V, Nicluescu-Duvaz I (1985) Spin labeled nitrosoureas. Potential anticancer agents. J Prakt Chem 327:667

Katritzky AR (1985) Advances in Heterocyclic Chemistry. Academic, London, 38:135

Kubota H, Kakefuda A, Okamoto Y, Fujii M, Yamamoto O, Yamgiwa Y, Orita M, Ikeda K, Takenchi M, Shibanuma T, Fsomura Y (1998) Spiro-substituted piperidines as neurokinin receptor antagonists. III. [1] Synthesis of (±)-N-[2-(3,4-dichlorophenyl)-4-(spiro-substituted piperidin-1'-yl)butyl]-N-methylbenzamides and evaluation of NK[1]-NK[2] dual antagonistic activities. Chem Pharm Bull 46:1538

Lewis GS, Nelson PH (1979) 3-[(1,2,3-Thiadiazol-5-ylthio)methyl] cephalosporins. J Med Chem 22:1214

Maruzella JC, Percival AH (1958) Antibacterial activity of essential oil vapors. J Am Pharm Assoc 47:471

Mokio IG, Soldatenkov AT, Federov VO, Ageev EA, Sergeeva ND, Lin S, Stashenku EE, Prostakov NS, Andreeva EL (1989) Antimicrobial activity of aliphatic-aromatic ketones, β-ketols and α-glycols. Khim Farm Zh 23:423

Noller CR, Baliah V (1948) The preparation of some piperidine derivatives by the Mannich reaction. J Am Chem Soc 70:3853

Pandiarajan K, Sekar R, Anantharaman R, Ramalingam V (1991) Conformational studies of some piperidin-4-ones using PMR spectroscopy. Indian J Chem 30B:490

Rovira C, Veciana J, Santalo N, Tarres J, Cirujeda J, Molins E (1994) Parallel synthesis of 1,2,3-thiadiazoles employing a "catch and release" strategy. J Org Chem 59:3307

Shafiee A, Lalezari I, Yazdani S, Shahbazian FM, Pontovi T (1973) Selenium Heterocycles VIII. Synthesis and antibacterial activity of selenosemicarbazide and 1,3,4-selenadiazolylcarbamic acid ester. J Pharm Sci 62:839

Smeets S, Dehaen W (1998) A novel way of preparing meso-substituted ethynylporphyrins and their derivatives by using 1,2,3-thiadiazole as a protecting group. Tetrahedron Lett 39:9841

Stanetty P, Kremslehner M (1998) Synthesis of Thieno[3,2-*d*][1,2,3]-thiadiazoles. New mechanistic aspects of the Hurd-Mori reaction. Heterocycles 48:259

Stanetty P, Kremslehner M, Mullner J (1996) Synthesis of annelated 1,2,3-thiadiazole derivates. J Heterocycl Chem 33:1759

Thomas EW (1984) In: Potts KT, Katritzky AR, Rees CW (eds) Comprehensive Heterocyclic Chemistry, Pergamon, London, 4B pp. 4476

Thomas EW, Nishizawa EE, Zimmermann DC, Williams J (1985) Synthesis and platelet aggregation inhibitory activity of 4,5-bis(substituted)-1,2,3-thiadiazoles. J Med Chem 28:442

Tumkevicius S, Labanauskas L, Bacinskaite V, Brukstus A, Urbelis G (2003) Synthesis and structure of benzimidazo[1,2-c][1,2,3]thiadiazoles: First examples of a novel ring system. Tetrahedron Lett 44:6635

Watson AA, Fleet GWJ, Asano N, Molyneux RJ, Nugh RJ (2001) Polyhydroxylated alkaloids. Natural occurrence and therapeutic applications. Phytochemistry 56:265