Bioorganic & Medicinal Chemistry Letters 21 (2011) 6301–6304

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis, stereochemistry and in vitro antimicrobial evaluation of novel 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-4-phenyl-2,3-dihydrothiazoles

Rajamanickam Ramachandran [a], Paramasivam Parthiban [a], Mannangatty Rani [b], Sampathkumar Jayanthi [c], Senthamaraikannan Kabilan [b], Yeon Tae Jeong [a,*]

[a] Department of Image Science and Engineering, Pukyong National University, Busan 608 737, Republic of Korea
[b] Department of Chemistry, Annamalai University, Annamalainagar 608 002, Tamil Nadu, India
[c] E.S. College of Engineering and Technology, Vilupuram 605 602, Tamil Nadu, India

ARTICLE INFO

Article history:
Received 4 August 2011
Revised 24 August 2011
Accepted 29 August 2011
Available online 1 September 2011

Keywords:
Hantzsch thiazoles
Azabicyclo[3.3.1]nonan-9-ones
Antibacterial activity
Antifungal activity
Stereochemistry

ABSTRACT

2-[(2,4-Diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-4-phenyl-2,3-dihydrothiazoles (**3a**–**3k**) have been synthesized by the cyclization of 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one thiosemicarbazones with phenacyl bromide and characterized by analytical (melting point and elemental analysis) and spectral (IR, ^{1}H NMR, ^{13}C NMR, D_2O exchange, NOESY and mass) techniques. The novel Hantzsch products (**3a**–**3k**) were screened for their in vitro antibacterial and antifungal activities against some selected microorganisms. Structure activity relationship (SAR) for the reported compounds was studied by comparing their MIC values with standard drugs (Streptomycin and Amphotericin B). The results show that **3e** against *Escherichia coli* and *Cryptococcus neoformans* **3i** against *Bacillus Subtilis*, **3b** against *Aspergillus flavus*, and **3k** against *Rhizopus* sp. were found to show significant growth inhibition.

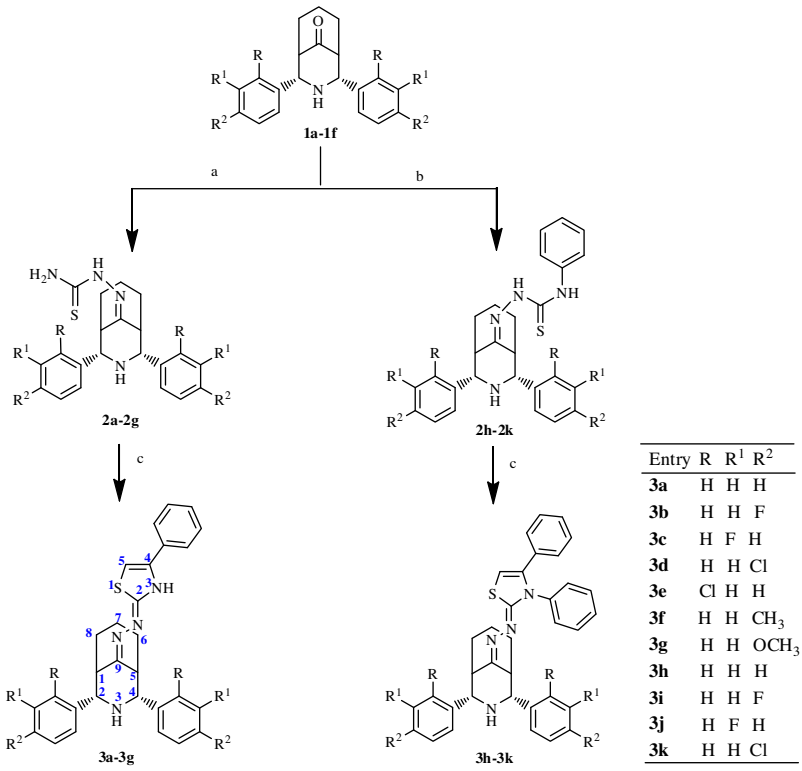
Substituted thiazoles are interesting building blocks, frequently encountered structural motifs in a variety of natural products, useful pharmaceuticals and plant protecting agents. The discovered compounds like epothilones[1] cystothiazoles[2] or thiazolyl peptide antibiotics[3] also contain at least one thiazole ring and show interesting biological activities. One of the oldest methods, as popular today as ever, involves the reaction of primary thioamides with α-halocarbonyl compounds (Hantzsch reaction).[4] Different thiazoles bearing compounds possess anti-inflammatory activity[5] and some are known to be used as pharmaceutical and agrochemical products.[6–11] Thiazole ring is present in the different biologically active products, such as Bleomycin and Tiazofurin (antineoplastic agents and anticancer),[12] Ritonavir (anti-HIV drug),[13] Fanetizole and Meloxicam (anti-inflammatory agents),[14,15] Nizatidine (antiulcer agent),[16] imidacloprid (insecticide) and Penicillin (antibiotic). On the other hand, piperidine is another important fragment in heterocyclic family which is naturally occurring from several alkaloids, is a key part of numerous drug candidates. A research in piperidine chemistry and synthesis of new molecules are interested by their biological importance.[17,18] During the recent decade, several thousands of piperidine compounds have been used in clinical and preclinical studies.[19]

In order to overcome the increasing complexity of anti infective therapies, new effective anti-microbial drugs are required. In the view of the above-mentioned facts and in continuation of our earlier interest in the synthesis of novel heterocycles,[20–23] we report herein the synthesis and antimicrobial evaluation of some novel structure hybrids incorporating both the piperidine and thiazole analogues together to give new hybrid structure like the title compounds.

The synthetic route of the Hantzsch thiazoles (**3a**–**3k**) is depicted in Scheme 1. The starting materials, 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones were prepared by one-pot multi-component reaction (MCR) of aldehyde, cyclohexanone and ammonium acetate (2:1:1 ratio).[24] The intermediate ketone upon condensation with thiosemicarbazide under acidic condition afforded 2,4-diaryl-3-aza-bicyclo[3.3.1]nonan-9-one thiosemicarbazones.[25] Finally, the target compounds 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-4-phenyl-2,3-dihydrothiazoles (**3a**–**3k**, Scheme 1) were arrived by the cyclization of key intermediate with phenacyl bromide under reflux condition (8 h at 80 °C). In order to find the optimum reaction condition and solvent, different solvents such as EtOH, MeOH, MeCN and CH_2Cl_2 were employed. It is noted that the reaction in methylene chloride afforded the target compounds in low yield (29%) whereas the reaction with polar aprotic solvents like EtOH, MeOH, CH_3CN and DMF afforded the compounds (**3a**–**3k**) in good yield (around 90, 65, 48 and 55% respectively).

* Corresponding author.
E-mail address: ytjeong@pknu.ac.kr (Y.T. Jeong).

0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.08.115



Entry	R	R^1	R^2
3a	H	H	H
3b	H	H	F
3c	H	F	H
3d	H	H	Cl
3e	Cl	H	H
3f	H	H	CH_3
3g	H	H	OCH_3
3h	H	H	H
3i	H	H	F
3j	H	F	H
3k	H	H	Cl

Scheme 1. Reagents and conditions: (a) $C_2H_5OH/NH_2NHCSNH_2/H^+$, Reflux, 8 h:(b) $C_2H_5OH/NH_2NHCSNHPh/H^+$, Reflux, 8 h; (c) $C_2H_5OH/PhCOCH_2Br/NaOAc$, Reflux, 8 h.

Similarly, an attempt has been made to increase the yield of target compounds by modifying the reaction conditions. The reactions were carried out with the following three reaction conditions, (i) with sodium acetate or acetic acid (ii) mixture of sodium acetate and acetic acid (iii) without sodium acetate or acetic acid were employed for cyclization. Of the three different reaction conditions, the reaction with mixture of sodium acetate and acetic acid afforded the target molecules **(3a**–**3k**) with good yield around 90%. The mixture of sodium acetate and acetic acid acts as buffer system to maintain the pH (around 5) of the reaction solution and avoid the C═N cleavage in hydrazones. During the course of reaction, excess of sodium acetate was used to scavenge the hydrogen bromide whereas acetic acid acts as the cyclizing agent. However, reactions without acetic acid and sodium acetate afforded **3a**–**3k** in poor yield (around 24%).

The structures of the synthesized compounds **(3a**–**3k)** were elucidated by IR, NMR, mass and elemental analysis. The physical and analytical data are given in Table S1 (Supplementary data). IR spectra of compounds **(3a**–**3e)** exhibit two strong absorption frequencies around 3300 and 3100 cm^{-1} due to NH stretching frequencies of piperidine and thiazole analogues whereas the C═N stretching frequency observed around 1600 and 1580 cm^{-1}. Aromatic and aliphatic C–H stretching vibrations are observed in the range of 2700–3100 cm^{-1}. The absences of C═S stretching band in the intermediate (2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one thiosemicarbazones) proved that the expected cyclization occurred in the thiosemicarbazone analogue. Moreover, the observed molecular ion peak (M^+) for compound **3d**, **3h**, and **3i** and elemental analysis (C H N analysis) of compounds **3a**–**3k** are well compatible with proposed molecular formula.

Further structural assignments were made by NMR analysis by considering compound **3d** as the representative compound. However, the benzylic proton signals appeared at 4.36 and 4.16 ppm, respectively, are assignable for H-2a and H-4a whereas the two bridgehead proton signals appeared at 2.62 and 2.85 ppm (H-1 and H-5, respectively). Further, there are two multiplets observed with three protons integral in the lower frequency region of 1.56–1.75 and 1.27–1.38 ppm. Of the two multiplets, one at 1.56–1.75 ppm is due to H-6e, H-8e and NH protons whereas another multiplet 1.27–1.38 ppm can be assigned to H-6a, H-8a and H-7e protons. Furthermore, the unassigned multiplet centered at 2.66 ppm is due to H-7a proton. The chemical shift variation between H-7a and H-7e (about 1.3 ppm) is due to non-bonded interaction ($A^{1,3}$ interaction, Fig. 1) between lone pair nitrogen in the piperidine ring and H-7a proton. Owing to this interaction, the carbon (C-7) gets partially negative charge and the proton (H-7a) acquires partially positive charge. Therefore, the proton signal is deshielded and carbon signal appeared in the shielded region. The observed two NH protons were confirmed by D_2O exchange analysis which shows that one of the NH proton signal (thiazole ring) is merged with aromatic protons while other one in the piperidine ring is merged with cyclohexane ring proton signals. Moreover, a collection of signal observed in the aromatic region 6.89–8.11 ppm (14 proton integral value) are due to aryl protons at 4th position of the thiazole ring and C-2 and C-4 position of the piperidine ring. However, a doublet at 7.75 ppm shows strong NOE (Fig. 1) with H-4a protons. Hence, 7.75 ppm signal should be due to *ortho* protons of C-2 and C-4 phenyl group. Similarly, signal at 6.89 ppm has NOE with 7.27 ppm (triplet) and 7.27 ppm has NOE with 7.38 ppm (multiplet). Therefore, the signals 6.89 (singlet), 7.38 (multiplet) and 7.27 ppm (triplet) are respectively assigned to C-5, NH and, *ortho* protons of C-4 phenyl group of thiazole ring.

In ^{13}C NMR spectrum of compound **3d**, two signals with equal intensities at 64.63 and 63.68 ppm are assigned to the benzylic carbons C-2 and C-4, respectively, whereas resonances at 45.58 and 38.84 ppm are assigned to C-1 and C-5 bridgehead carbons, respectively. The ring methylene carbons C-6, C-7 and C-8 are appeared at 26.36, 21.28 and 27.97 ppm, respectively. Furthermore, two carbon signals observed in the higher frequency region of 170.01 and 159.26 ppm with less intensity. Of the two signals, highly

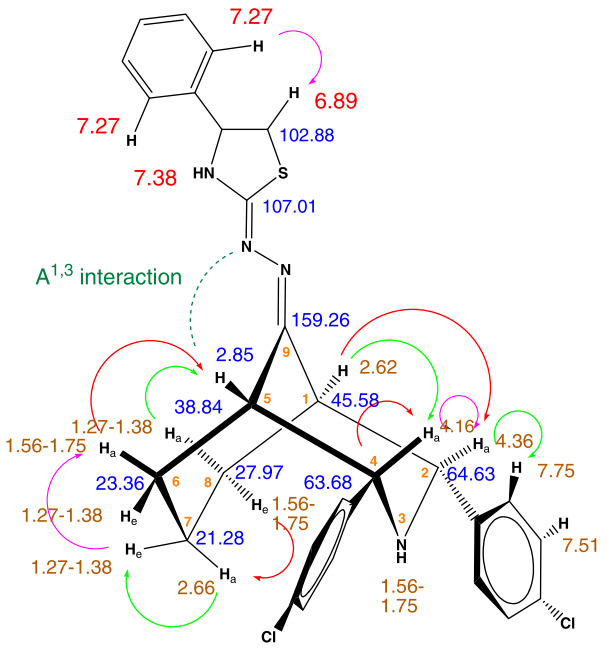


Figure 1. Selected NOE correlations and $A^{1,3}$ interaction.

deshielded (170.01 ppm) signal is due to C-5 carbon in thiazole. This is due to the presence of adjacent nitrogen and sulphur groups, another one signal (159.26) is due to C-9 carbon. By the DEPT spectrum of compound **3a**, the signal at 102.88 ppm is unambiguously assigned to the methine carbon of thiazole ring.

As stated earlier, the position and orientation of the ring protons are confirmed by nuclear overhauser effect (NOE) correlation (Fig. 1). Moreover, most of the signals resonated as singlets. Therefore, conformation of two six-membered rings were successfully derived with the support of chemical shift parameters and NOE correlations. However, the strong NOEs between H-1 and H-2 and also between H-1 and H-4 clearly confirm that the benzylic and bridgehead protons occupy axial and equatorial dispositions, respectively. Similarly, the H-7a proton has strong NOE with H-7e proton and its adjacent equatorial protons. This NOE states that the signal at 1.56–1.78 ppm is due to equatorial protons. Besides, H-5 proton has NOE with H-8a and H-6a protons. Hence, the bridgehead protons (H-5) also occupy equatorial position. Therefore, the NOE analysis clearly suggest that the two six-membered rings adopt the chair conformation.

Table 1
Antibacterial activity of compounds **3a**–**3k** against some antibacterial strains (MIC in μg/mL)

Entry	Minimum inhibitory concentration (MIC) in μg/mL				
	S. aureus	*B. Subtilis*	*S. typhi*	*E. coli*	*K. pneumoniae*
3a	25	200	100	—	100
3b	200	12.5	50	50	12.5
3c	12.5	—	200	25	25
3d	25	25	50	100	100
3e	100	12.5	25	6.25	100
3f	200	50	200	12.5	200
3g	25	—	—	100	200
3h	25	100	100	200	—
3i	12.5	6.25	50	100	100
3j	50	100	12.5	12.5	100
3k	25	12.5	25	100	—
Streptomycin	50	12.5	50	12.5	25

— No inhibition even at maximum concentration (200 μg/mL).

In order to study the potency of inhibition of 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-4-phenyl-2,3-dihydrothiazoles (**3a**–**3k**) by in vitro method. The phenyl ring C-2 and C-4 of the piperidine ring substituted with different groups. Compounds **3a**–**3k** were assessed to elicit their antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Salmonella typhi, Escherichia coli* and *Klebsiella pneumonia* and antifungal activity against *Cryptococcus neoformans, Candida albicans, Rhizopus* sp., *Aspergillus niger* and *Aspergillus flavus.* The solvent DMSO is used as control which did not show any inhibition against tested microorganisms. The activity of compounds in terms of minimum inhibitory concentrations (MIC in μg/mL) along with reference drugs, Streptomycin (for bacterial activity) and Amphotericin B (for fungal activity) are displayed in Tables 1 and 2, respectively. The investigated compounds showed different degrees of antimicrobial activity in relation to the tested microbial species. The extent of antimicrobial activity depended on the microorganism and the type of functional groups present in the molecule.

In order to get more insight into the structure–activity relationship, we incorporated electron donating and withdrawing substituent on the phenyl group at 2,4-positions in piperidine ring. Among the compounds tested for antibacterial activity, compound **3a** (unsubstituted phenyl group) showed poor to moderate inhibition activity (25–200 μg/mL) against the tested organisms. Moreover, compound **3a** did not show bacterial inhibition even at maximum concentration (200 μg/mL). But, introduction of the halogen function (fluoro group) at the *para* position of the phenyl group in piperidine ring (compound **3b**) elevated the growth

Table 2
Antifungal activity of compounds **3a**–**3k** against some antifungal strains (MIC in μg/mL)

Entry	Minimum inhibitory concentration (MIC) in μg/mL				
	C. neoformans	*C. albicans*	*Rhizopus* sp.	*A. niger*	*A. flavus*
3a	100	200	200	50	—
3b	100	100	50	12.5	6.25
3c	50	100	—	200	100
3d	200	200	50	25	25
3e	6.25	25	100	100	50
3f	—	200	12.5	50	200
3g	12.5	100	100	25	12.5
3h	50	12.5	200	200	100
3i	—	12.5	50	100	200
3j	200	12.5	100	25	200
3k	50	100	6.25	25	100
Amphotericin B	25	25	25	50	50

— No inhibition even at maximum concentration (200 μg/mL).

inhibition activity by four and two fold against *B. subtilis* and *K. pneumonia*, respectively, and moderate activity (50 μg/mL) was observed against *E. coli and S. typhi*. Similarly, introduction of fluoro function at the *meta* position of the 2,4-diphenylpiperidine ring (compound **3c**), demonstrated significant inhibition growth at 12.5 μg/mL against *S. aureus* but against *B. subtilis* did not showed bacterial activity even at maximum concentration (200 μg/mL). The replacement of *para* fluorophenyl group (compound **3b**) by *para* chlorophenyl group (compound **3d**) decreases the inhibition activity against all the tested bacterial strains. Modification of position of chloro function from *para* to *ortho* in 2,4-diphenylpiperidine ring (compound **3e**) registered a significant activity against *E. coli* (6.25 μg/mL) and *B. subtilis* (12.5 μg/mL). Moreover, the observed activity (compound **3e** against *E. coli*) is one fold higher than that of the standard drug (Streptomycin). Electron withdrawing substituents like fluoro and chloro substituted 2,4-diarylpiperidines or 2,4-disubstituted piperidine derivatives exerted excellent antibacterial and antifungal activities.[21,23] Fluorination increases the lipophilicity due to strong electron withdrawing capability of fluorine.[26] Moreover, fluorine substitution was commonly used in contemporary medicinal chemistry to improve metabolic stability, bioavailability and protein ligand interactions.[27] Compounds **3f** and **3g** with electron donating methyl and methoxy substitutions, respectively, show minimum to moderate antibacterial activity against all the tested bacterial strains in the range of 12.5–200 μg/mL except **3f** against *E. coli* which shows good inhibition activity. Moreover, by the introduction of one more phenyl group in the nitrogen site of thiazole ring (compound **3h**) moderate activity was noted. Compounds (**3i**, **3j**, and **3k**) having electron withdrawing substituent at the phenyl group in C-2 and C-4 of piperidine ring and one more phenyl group at the nitrogen site of thiazole ring registered significant bacterial activity (i.e., compound **3i** against *S. aureus* and *B. subtilis*, **3j** against *S. typhi* and *E. coli* and **3k** against *B. subtilis* in the range of 6.25–12.5 μg/mL).

Further, the in vitro antifungal activity of all the compounds (**3a–3k)** were examined against five pathogenic fungal strains viz. *C. neoformans*, *C. albicans*, *Rhizopus* sp., *A. niger* and *A. flavus*. The obtained MIC values of the tested compounds and standard are depicted in Table 2. Compounds (**3a** and **3h**) with unsubstitution at the phenyl group exhibit the activity in the range of 50–200 μg/mL except compound **3h** against *C. albicans*, which shows the inhibition activity at 12.5 μg/mL. Moreover, compounds **3a**, **3c** and **3f/3i** were totally inactive (even at 200 μg/mL) against *A. flavus*, *Rhizopus* sp. and *C. neoformans*, respectively. Substitution of fluoro function in 2,4-diphenylpiperidine moiety of compounds **3a** and **3h** (compound **3b** and **3i**) has an impact on antifungal activity. A good inhibition activity was observed for compound **3b** against *A. niger* (12.5 μg/mL) and *A. flavus* (6.25 μg/mL) and compound **3i** against *C. albicans* (12.5 μg/mL). A modification of position of fluoro function in compounds **3b** and **3i** (compounds **3c** and **3j**) has influence on the antifungal activity. The inhibition activity of the compound **3c** against the tested fungal organism found to be decreased by three to four folds but against *C. neoformans* the activity increased by one-fold. Akin to the antibacterial activity, introduction of methyl or methoxy group in the phenyl rings, minimum to moderate activity was noted (25–200 μg/mL). But, compounds **3f** against *Rhizopus* sp. and **3g** against *C. neoformans* and *A. flavus* which enhanced the biological activity remarkably and MIC values found to be 12.5 μg/mL.

In conclusion, a close examination of in vitro antibacterial and antifungal activities of variously substituted 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-4-phenyl-2,3-dihydrothiazoles against the tested bacterial and fungal strains provided a better structure–activity correlation. Of the tested compounds, those with fluoro function at C-2 and C-4 phenyl group exerted highest level of antibacterial and antifungal activities. Thus, in future, this class of thiazoles derivatives may be used as templates to generate better drugs to fight bacterial and fungal infections.

Supplementary data

Supplementary data (the detailed experimental and spectral data (IR, ^{1}H NMR and ^{13}C NMR) for all the synthesized compounds (**3a-3k**) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.08.115.

References and notes

1. (a) Hoefle, G.; Bedorf, N.; Gerth, K.; Reichenbach, H. Ger. Offen. DE 4138042 A1 19930527, 1993.; (b) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325.
2. (a) Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S. *J. Antibiot.* **1998**, *51*, 275; (b) Suzuki, Y.; Ojika, M.; Sakagami, Y.; Fudou, R.; Yamanaka, S. *Tetrahedron* **1998**, *54*, 11399; (c) Riego, E.; Hernández, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, 1907.
3. (a) Selva, E.; Beretta, G.; Montanini, N.; Saddler, G. S.; Gastaldo, L.; Ferarri, P.; Lorenzetti, R.; Landini, P.; Ripamonti, F.; Goldstein, B. P.; Berti, M.; Montanaro, L.; Denaro, M. *J. Antibiot.* **1991**, *44*, 693; (b) Kettenring, J.; Colombo, L.; Ferrari, P.; Tavecchia, P.; Nebuloni, M.; Vekey, K.; Gallo, G. G.; Selva, E. *J. Antibiot.* **1991**, *44*, 702; (c) Selva, E.; Ferrari, P.; Kurz, M.; Tavecchia, P.; Colombo, L.; Stella, S.; Restelli, E.; Goldstein, B. P.; Ripamonti, F.; Denaro, M. *J. Antibiot.* **1995**, *48*, 1039.
4. (a) Hantzsch, A.; Weber, J. H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118; (b) Bauer, W.; Kühlein, K. In *Houben-Weyl's Methoden der Organischen Chemie*; Georg Thieme Verlag: Stuttgart, New York, 1985; Vol. E85, p 1218; (c) Liebscher, J. *Houben-Weyl's Methoden der Organischen Chemie* In *Vol. E8b*; Georg Thieme Verlag: Stuttgart, 1994. Teil 2, pp 1–399.
5. Sharma, P. K.; Swonhney, S. N.; Gupta, A.; Singh, G. B.; Bani, S. *Indian J. Chem.* **1998**, *37B*, 371.
6. Beck, G.; Heitzer, H. U.S. Patent 4,748,243, May 31, 1988.
7. Osaka, H. U.; Matsubara, N. H.; Kawabe, I. M. U.S. Patent 5,180,833, Jan 19, 1993.
8. Schulze, K.; Richter, F.; Seisheit, R.; Krause, R.; Muhlstadt, M.; Darstellung, Z.; Vinylsenfölen, C. V. *J. Prakt. Chemie.* **1980**, *322*, 629.
9. Murugan, R.; Scriven, E. F. V. PCT Int. Appl. WO 9,845,279, Oct 15, 1998; *Chem. Abstr.* **1998**, *129*, 302633v.
10. Jackson, A.; Heyes, G.; Grayson, J. I.; Clarke, R. U.S. Patent 5,705,652, 1998.
11. Leanna, R. M.; Morton, H. E. PCT Int. Appl. WO 9,616,050,30, 1996; *Chem. Abstr.* **1996**, *125*, 114603d.
12. Grifantini, M. *Curr. Opin. Invest. Drugs* **2000**, *1*, 257.
13. Kempf, D. J.; Marsh, K. C.; Denissen, J. F.; McDonald, E.; Vasavanonda, S.; Flentge, C. A.; Green, B. E.; Fino, L.; Park, C. H.; Kong, X. P.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H. L.; Robins, T.; Stewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard, J. M.; Norbeck, D. W. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2484.
14. Lednicer, D.; Mitscher, L. A.; George, G. I. In *Organic Chemistry of Drug Synthesis*; Wiley: New York, 1990; Vol. 4, p 95.
15. Rehman, M. Z.; Anwar, C. J.; Ahmad, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 1771.
16. Knadler, M. P.; Bergstrom, R. F.; Callaghan, J. T.; Rubin, A. *Drug Metab. Dispos.* **1986**, *14*, 175.
17. (a)*Pharmaceutical Substances*; Kleemann, A., Engel, J., Kutscher, B., Reichert, D., Eds.; Thieme: Stuttgart, 1999; (b) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine, Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991.
18. (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953; (b) Kouznetsov, V. V. *Khim.-Farm. Zh.* **1991**, *25*, 61–75, *Chem. Abstr.* **1991**, *115*, 158.846h.; (c) Vartanyan, R. S. *Khim.-Farm. Zh.* **1983**, *17*, 540–550, *Chem. Abstr.* **1983**, *99*, 53629n.
19. Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.
20. Aridoss, G.; Amirthaganesan, S.; Kumar, N. A.; Kim, J. T.; Lim, K. T.; Kabilan, S.; Jeong, Y. T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6542.
21. Ramachandran, R.; Rani, M.; Kabilan, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2819.
22. Parthiban, P.; Aridoss, G.; Rathika, P.; Ramkumar, V.; Kabilan, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6981.
23. Rani, M.; Ramachandran, R.; Kabilan, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6637.
24. Baliah, V.; Jeyaraman, R. *Indian J. Chem.* **1971**, *9*, 1020.
25. Ramachandran, R.; Rani, M.; Kabilan, S. *J. Mol. Struct.* **2010**, *970*, 42.
26. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3.
27. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.