Design, synthesis, characterization and antitubercular activity of some 2-heterocycle-substituted phenothiazines

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Abstract

Some novel 2-heterocycle-substituted phenothiazines having a pyrazolo[3,4-*d*]pyrimidine nucleus have been synthesized by using the Biginelli multi-component cyclocondensation reaction. The products were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. The products were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H_{37} Rv.

Keywords: Phenothiazine, cyclocondensation, pyrazolo[3,4-*d*]pyrimidine

Introduction

The chemistry of nitrogen-sulfur heteroatom containing aromatic compounds is becoming more popular as an area of research. Phenothiazines and related compounds have shown diverse biological activities including as tranquilizers,[1] anti-inflammatory,[2] antimalarial,[3] antipsychotropic,[4] antimicrobial,[5] antitubercular,[6,7] antitumour[8-10] and stimulation of the penetration of anticancer agents *via* the blood-brain barrier. They bind to physiological targets or receptors, producing many possible mechanisms of actions. However, solid cancers of the brain and stomach are generally resistant to chemotherapeutic agents.[11] Phenothiazines are inexpensive and widely available, and therefore have been examined as anticancer drugs.

A slight variation in the substitution pattern on the phenothiazine nucleus often causes a marked difference in activities and therefore phenothiazines with various substituents are being synthesized and tested for activities in search of better medicinal agents. It has been reported[12] that some phenothiazines inhibit intracellular replication of viruses including human immunodeficiency viruses (HIV). Furthermore, some of these derivatives have been reported to exhibit significant anticancer activities[13,14] and great interest has arisen in the design and synthesis of new phenothiazines to explore their anticancer activities. The pyrimidine nucleus,

which has a useful structure for further molecular exploration for the development of new derivatives with different biological activities, has received much attention in recent years.[15]

Pyrimidine derivatives are of interest because of their pharmacological properties[15-26] including antiviral,[16] antitumour,[19] antibacterial[20-24] and antihypertensive[18] effects. Several synthetic strategies have been reported for the preparation of pyrimidine derivatives.[24,27-33] Most of these are based on modification of the classical one-pot Biginelli reaction[24,28-32] and in some cases on more complex multi-step processes,[33,34] which may involve the use of some expensive and commercially non-available materials. Owing to the versatility of pyrimidines and as a continuation of our previous work,[35] we have extended the convenient Biginelli reaction to include some pyrimidine derivatives containing a phenothiazine nucleus.

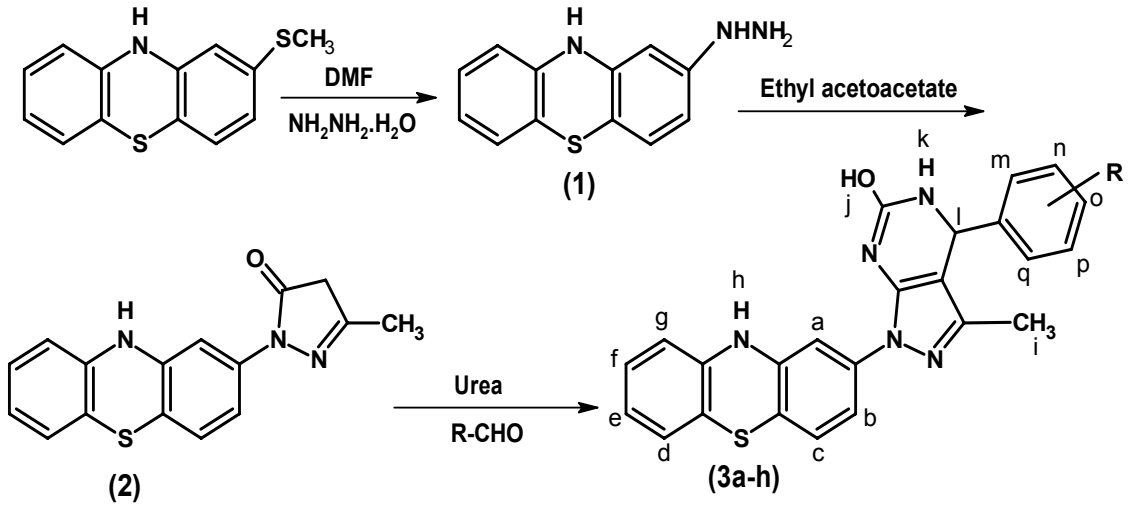
Results and Discussion

Chemistry

The classical three-component Biginelli condensation is usually carried out in alcoholic solution containing a few drops of concentrated hydrochloric or sulfuric acid as catalyst, although other systems such as THF/HCl, dioxane/HCl, or acetic acid/HCl have also been employed.[36] One major drawback of the classical Biginelli protocol is the low yield that is frequently encountered when using sterically more demanding aldehydes or 1,3-dicarbonyl compounds.[36]

In order to promote conditions that would favor higher yields of products, we have recently performed Biginelli condensations using different catalysts such as PPA, $AlCl_3$, BF_3 etc. We found that using phosphorus pentoxide as a catalyst in the Biginelli one-pot protocol, gave a significant increase in the yields of DHPMs, especially for systems that give only moderate yields using traditional Biginelli conditions.

Several pyrimidine derivatives containing a phenothiazine nucleus were synthesized at reflux temperature. Reaction of 5-methyl-2-(10*H*-phenothiazin-2-yl)-2,4-dihydro-3*H*-pyrazol-3-one **(2)**, an appropriate aldehyde, urea and phosphorus pentoxide under reflux conditions afforded 3-methyl-1-(10*H*-phenothiazin-2-yl)-4-phenyl-6-hydroxy-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidines **(3a-h)** (Scheme 1). The yields of the products were found to be excellent (80-90%). The structures of the synthesized compounds were assigned on the basis of IR, ^{1}H NMR spectra, ^{13}C NMR, mass spectra and purity proven by elemental analysis. In the ^{1}H NMR spectra of **(3a-h)** a sharp peak representing the methine proton of the pyrimidine was observed in the range of 5.12-5.28 δ confirming the formation of the pyrazolo[3,4-*d*]pyrimidine nucleus.



Sr. No.	R	m	n	o	p	q
3a	H	H	H	H	H	H
3b	2-OH	OH	H	H	H	H
3c	4-OH	H	H	OH	H	H
3d	2-Cl	Cl	H	H	H	H
3e	4-Cl	H	H	Cl	H	H
3f	2-NO_2	NO_2	H	H	H	H
3g	3-NO_2	H	NO_2	H	H	H
3h	4-OCH_3	H	H	OCH_3	H	H

Scheme 1

Antitubercular activity

The antitubercular activity of the compounds was assessed at the Tuberculosis Antimicrobial Acquisition and Co-ordination Facility (TAACF), U.S.A. Primary screening of the compounds was conducted at >6.25 μg/ml against *Mycobacterium tuberculosis* H_{37} Rv in BECTEC 12B medium using the BACTEC 460 radiometric system. The antitubercular activities are represented in Table 1.

Table 1. Antitubercular activity of **3a-h**

Sr. No.	R	Molecular formula	MIC	% Inh	Activity
3a	H	$C_{24}H_{20}N_6S$	>6.25	79	-
3b	2-OH	$C_{24}H_{20}N_6OS$	>6.25	75	-
3c	4-OH	$C_{24}H_{20}N_6OS$	<6.25	94	+
3d	2-Cl	$C_{24}H_{20}N_6SCl$	<6.25	92	+
3e	4-CI	$C_{24}H_{20}N_6SCl$	<6.25	94	+
3f	2-NO_2	$C_{24}H_{19}N_7O_2S$	>6.25	74	-
3g	3-NO_2	$C_{24}H_{19}N_7O_2S$	>6.25	77	-
3h	4-OCH_3	$C_{25}H_{22}N_6OS$	>6.25	63	-

By visualizing the antitubercular data, it could be observed that all the compounds displayed mild to moderate activity. Compounds **3c**, **3d** and **3e** were found to be particularly active against *Mycobacterium tuberculosis* H_{37} Rv strain.

Conclusions

In conclusion, we have developed a simple and efficient method for the synthesis of pyrimidines having a phenothiazine nucleus. We also believe that the procedural simplicity, the efficiency and the easy accessibility of the reaction partners gives access to a wide array of heterocyclic frameworks equipped with a pendant phenothiazine unit. Other compounds of this group are presently under investigation.

Experimental Section

General Procedures. All chemicals were purchased from Aldrich Chemicals (Mumbai, India) and were used without further purification. Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC using Silica G and the spots were exposed to iodine vapour for visualization. ^{1}H NMR spectra were obtained in $CDCl_3$ solution on a Bruker DPX 300 MHz spectrometer. ^{13}C-NMR (75 and 125 MHz) spectra were measured on a Bruker AC 200, DPX 300 and ARX 500, at 25 °C, in $CDCl_3$. IR spectra were recorded on a Shimadzu 8400 spectrometer in KBr (γ in cm^{-1}). Elemental analyses of the newly synthesized compounds were carried out on Carlo Erba 1108 analyzer.

Synthesis of 2-hydrazinophenothiazine (1). A mixture of 2-methylthiophenothiazine 2.45 gm (0.01 mol) and hydrazine hydrate (10 ml) was refluxed for 8 h. The reaction mixture was poured in to ice cold water; the crude product was filtered, dried and recrystallized from 95% ethanol. Yield 82%, mp. 122-124 ºC. IR (KBr): 3335 (NH), 653 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ

7.45-7.76 (m, 7H, Ar-H), 9.15 (s, 1H, NH), 7.86-7.95 (m, 3H, $NHNH_2$); ^{13}C-NMR ($CDCl_3$): δ 103, 103.5, 107, 114.4, 116.8, 122.3, 127.2, 128.3, 142.3, 143, 150.6. Mass (*m/z*): 229. Anal. (%) for $C_{12}H_{11}N_3S$, Calcd. C, 62.86; H, 4.84; N, 18.33. Found: C, 62.82; H, 4.80; N, 18.30.

Synthesis of 5-methyl-2-(10*H*-phenothiazin-2-yl)-2,4-dihydro-3*H*-pyrazol-3-one (2). A mixture of 2-hydrazinophenothiazine 2.29 g (0.01 mol) and ethyl acetoacetate 1.3 ml (0.01 mol) in 30% w/w sodium ethoxide (20 ml) was heated under reflux for 12 h. The reaction mixture was poured into ice cold water; the crude product was filtered, dried and recrystallized from 95% ethanol. Yield 68%, mp. 111-113 ºC. IR (KBr): 3330 (NH), 650 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.66-7.90 (m, 7H, Ar-H), 9.03 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ 16.7, 42.4, 111.3, 111.8, 112.1, 114.4, 116.4, 122.3, 127.1, 128.2, 139.6, 142.5, 162.7, 174.1. Mass (*m/z*): 229. Anal. (%) for $C_{12}H_{11}N_3S$, Calcd. C, 62.86; H, 4.84; N, 18.33. Found: C, 62.82; H, 4.80; N, 18.30.

General procedure for synthesis of compounds 3a-h. 3-Methyl-1-(10*H*-phenothiazin-2-yl)-4-phenyl-6-hydroxy-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (3a)

A mixture of benzaldehyde 1.06 ml (0.01 mol), 5-methyl-2-(10*H*-phenothiazin-2-yl)-2,4-dihydro-3*H*-pyrazol-3-one 2.95 gm (0.01 mol), urea 0.76 gm (0.01 mol) and phosphorus pentoxide (200 mg) in 95 % ethanol (30 ml) was heated under refluxed condition for 5 hours. After cooling to rt., the crystalline product was filtered and recrystallized from ethanol. Yield 74%, mp. 181-183 ºC. IR (KBr): 3330 (NH), 1615 (C = N), 1642 (C-N), 651 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (S, 3H, H_i), 5.12 (S, 1H, H_l), 7.42-7.68 (m, 12H, $H_{a\text{-}g,\ m\text{-}q}$), 8.42 (s, 1H, H_h), 9.11 (s, 1H, H_k); ^{13}C-NMR ($CDCl_3$): δ 26.3, 41.1, 52.3, 60.1, 103.1, 103.7, 104.9, 114.2, 116.7, 122.1, 126, 127.1, 127.7, 128.1, 128.9, 136.1, 142.1, 143.3, 155.1, 164. Mass (*m/z*): 425. Anal. (%) for $C_{24}H_{19}N_5OS$, Calcd. C, 67.74; H, 4.50; N, 16.46. Found: C, 67.70; H, 4.47; N, 16.41.

3-Methyl-1-(10*H*-phenothiazin-2-yl)-4-(2-hydroxyphenyl)-6-hydroxy-4,5-dihyd-ro-1*H*-pyrazolo[3,4-*d*]pyrimidine (3b). Yield 79%, mp. 150-152 ºC, IR (KBr): 3333 (NH), 1613 (C = N), 1640 (C-N), 655 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H, H_i), 5.20 (s, 1H, H_l), 7.62-8.12 (m, 11H, $H_{a\text{-}g,\ n\text{-}q}$), 8.35 (s, 1H, H_h), 9.15 (s, 1H, H_k), 10.08 (s, 1H, H_m); ^{13}C-NMR ($CDCl_3$): δ 26.4, 34.4, 52.8, 60, 103.2, 103.7, 105.1, 114.4, 115.7, 116.6, 121.3, 122.3, 127.1, 127.4, 127.7, 128.3, 142.3, 143.1, 155.1, 155.7, 162.9. Mass (*m/z*): 441. Anal. (%) for $C_{24}H_{19}N_5O_2S$, Calcd. C, 65.29; H, 4.34; N, 15.86; Found: C, 65.25; H, 4.38; N, 15.83.

3-Methyl-1-(10*H*-phenothiazin-2-yl)-4-(4-hydroxyphenyl)-6-hydroxy-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (3c).Yield 81%, mp. 169-171 ºC, IR (KBr): 3328 (NH), 1612 (C = N), 1642 (C-N), 645 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, H_i), 5.26 (s, 1H, H_l), 7.13-7.38 (m, 7H, $H_{a\text{-}g}$), 7.40-7.43 (dd, 2H, H_{mn}, J = 9 Hz), 8.07-8.10 (dd, 2H, H_{pq}, J = 9 Hz), 8.35 (s, 1H, H_h), 9.09 (s, 1H, H_k), 10.15 (s, 1H, H_o); ^{13}C-NMR ($CDCl_3$): δ 26.4, 41.3, 52.6, 59.6, 103.1, 103.8, 105.1, 114.3, 115.9, 116.7, 122.1, 127.1, 127.7, 128, 128.3, 142.1, 143.2, 155.4, 155.7, 162.8. Mass (*m/z*): 441. Anal. (%) for $C_{24}H_{19}N_5O_2S$, Calcd. C, 65.29; H, 4.34; N, 15.86; Found: C, 65.30; H, 4.32; N, 15.80.

3-Methyl-1-(10*H*-phenothiazin-2-yl)-4-(2-chlorophenyl)-6-hydroxy-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (3d). Yield 77%, mp. 186-188 ºC, IR (KBr): 3325 (NH), 1610 (C = N), 1648 (C-N), 647 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, H_i), 5.23 (s, 1H, H_l), 7.63-7.86 (m, 11H, $H_{a\text{-}g,\ n\text{-}q}$), 8.39 (s, 1H, H_h), 9.16 (s, 1H, H_k); ^{13}C-NMR ($CDCl_3$): δ 26.1, 36.6, 52.1, 60.1, 103.1, 103.8, 104.9, 114.2, 116.8, 122.1, 126.7, 127.1, 127.5, 128.2, 129, 129.6, 133.2, 139.6, 142.1, 143.2, 155.3, 162. Mass (*m/z*): 460. Anal. (%) for $C_{24}H_{18}N_5OSCl$, Calcd. C, 62.67; H, 3.94; N, 15.23; Found: C, 62.65; H, 3.93; N, 15.20.

3-Methyl-1-(10*H*-phenothiazin-2-yl)-4-(4-chlorophenyl)-6-hydroxy-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (3e). Yield 76% mp. 153-155 ºC. IR (KBr): 3328 (NH), 1611 (C = N), 1647 (C-N), 651 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, H_i), 5.25 (s, 1H, H_l), 7.32-7.34 (dd, 2H, H_{mn}, J = 8.10 Hz), 7.81-7.84 (dd, 2H, H_{pq} J = 7.80 Hz), 7.88-8.27 (m, 7H, $H_{a\text{-}g}$), 8.43 (s, 1H, H_h), 9.09 (s, 1H, H_k); ^{13}C-NMR ($CDCl_3$): δ 26, 41.1, 52.1, 59.8, 103.2, 104, 105.1, 114.3, 116.4, 122.5, 127.1, 127.7, 128, 128.4, 128.9, 131.4, 134.4, 142.2, 143.1, 155.4, 162.8. Mass (*m/z*): 460. Anal. (%) for $C_{24}H_{18}N_5OSCl$, Calcd. C, 62.67; H, 3.94; N, 15.23; Found: C, 62.66; H, 3.90; N, 15.25.

3-Methyl-1-(10*H*-phenothiazin-2-yl)-4-(2-nitrophenyl)-6-hydroxy-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (3f). Yield 85%, mp. 213-216 ºC, IR (KBr): 3339 (NH), 1605 (C = N), 1645 (C-N), 657 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, H_i), 5.18 (s, 1H, H_l), 7.25-7.58 (m, 11H, $H_{a\text{-}g,\ n\text{-}q}$), 8.29 (s, 1H, H_h), 9.22 (s, 1H, H_k); ^{13}C-NMR ($CDCl_3$): δ 26.6, 36.3, 51.3, 59.5, 103.1, 103.7, 104.9, 114.3, 116.8, 122, 124.8, 126.6, 127.1, 127.8, 128, 129.1, 134, 135, 142.2, 143.2, 148.2, 155.5, 163. Mass (*m/z*): 470. Anal. (%) for $C_{24}H_{18}N_6O_3S$, Calcd. C, 61.27; H, 3.86; N, 17.86; Found: C, 61.25; H, 3.85; N, 17.84.

3-Methyl-1-(10*H*-phenothiazin-2-yl)-4-(3-nitrophenyl)-6-hydroxy-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (3g). Yield 73%, mp. 189-191 ºC, IR (KBr): 3336 (NH), 1612 (C = N), 1651 (C-N), 657 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$), delta (ppm), 2.33 (s, 3H, H_i), 5.15 (s, 1H, H_l), 7.72-7.95 (m, 11H, $H_{a\text{-}g,\ m,\ o\text{-}q}$), 8.36 (s, 1H, H_h), 9.19 (s, 1H, H_k); ^{13}C-NMR ($CDCl_3$): δ 26.3, 40.3, 52.6, 59.6, 103.1, 103.7, 105.1, 114.2, 116.2, 121.1, 122.3, 127.1, 127.8, 128, 129.9, 134.1, 140.5, 142.1, 143.5, 147.9, 155.1, 163.2. Mass (*m/z*): 470. Anal. (%) for $C_{24}H_{18}N_6O_3S$, Calcd. C, 61.27; H, 3.86; N, 17.86; Found: C, 61.23; H, 3.83; N, 17.82.

3-Methyl-1-(10*H*-phenothiazin-2-yl)-4-(4-methoxyphenyl)-6-hydroxy-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (3h). Yield 73%, mp. 206-209 ºC, IR (KBr): 3333 (NH), 1616 (C = N), 1657 (C-N), 650 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H, H_i), 5.28 (s, 1H, H_l), 7.31-7.33 (dd, 2H, H_{mn}, J = 7.80 Hz), 7.81-7.84 (dd, 2H, H_{pq}, J = 7.80 Hz), 7.89-7.99 (m, 7H, $H_{a\text{-}g}$), 8.33 (s, 1H, H_h), 9.06 (s, 1H, H_k); ^{13}C-NMR ($CDCl_3$): δ 26.5, 40.1, 52.3, 60.3, 103.1, 103.7, 104.8, 114.2, 116.3, 122.1, 126.5, 127.9, 128.7, 129.5, 133.2, 135.9, 142.1, 143.1, 149.2, 155.8, 163.5. Mass (*m/z*): 455. Anal. (%) for $C_{25}H_{21}N_5O_2S$, Calcd. C, 65.92; H, 4.65; N, 15.37; Found: C, 65.90; H, 4.60; N, 15.33.

References

1. El-Said, M. K. *Pharmazie* **1981**, *36*, 678.
2. Tilak, S. R.; Tyagi, R.; Goel, B.; Saxena, K. K. *Indian drugs* **1998**, *35*, 221.
3. Dominguez, J. N.; Lopez, S.; Charris, J.; Iarruso, L.; Lobo, G.; Semenow, A.; Olson, J. E.; Rosenthal, P. J. *J. Med. Chem*. **1997**, *40*, 2726.
4. Lin, G.; Midha, K. K.; Hawes, E. M. *J. Heterocycl.Chem*. **1991**, *28*, 215.
5. Raval, J.; Desai, K. K. *ARKIVOC* **2005**, *(xiii)*, 21.
6. Viveros, M.; Amaral, L. *Int. J. Antimicrob. Ag.* **2001**, *17*, 225.
7. Amaral, L.; Kristiansen. *Int. J. Antimicrob. Ag.* **2000**, *14*, 173.
8. Motohasho, N.; Kurihara, T.; Satoh, K.; Sakagami, H. H.; Mucsi, I.; Pusztai, R.; Szabo, M; Molnar, J. *Anticancer Res.* **1999**, *19*, 1837.
9. Motohasho, N.; Kawase, M.; Saito, S.; Sakagami, H. *Curr. Drug Targets* **2000**, *1*, 237.
10. Kurihara, T.; Motohasho, N.; Pang, G. L.; Higano, M.; Kiguchi, K.; Molnar, J. *Anticancer Res.* **1996**, *16*, 2757.
11. Ghosh, N.; Chattopadhyay, U. *In Vivo* **1993**, *7*, 435.
12. Floyd, R. A.; Scheider, J. E.; Zhu, Y. Q.; North, T. W.; Schinazi, F. *Proc. Am. Assoc. Cancer. Res*. **1993**, *34*, 359.
13. Kurihara, T.; Motohashi, N.; Sakagami, H. H.; Molnar J. *Anticancer Res.* **1999**, *19*, 4081.
14. Kurihara, T.; Nojima, K.; Sakagami, H.; Motohashi, N.; Molnar J. *Anticancer Research* **1999**, *19*, 3895.
15. Foroughifar, N.; Mobinikhaledi, A.; Shariatzadeh, S.M.; Masoudnia, M. *Asian J. Chem.* **2002**, *14*, 782.
16. Verma, R. S. *Green Chem*. **1999**, *43*.
17. Funahashi, K.; Satha, F.; Morita, M.; Noguchi, T. *J. Med. Chem*. **1989**, *32*, 2399.
18. Atwal, K. S.; Swanson, B. N.; Unger, S.E.; Floyd, D.M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem*. **1991**, *34*, 806.
19. Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803.
20. Xie, W.; Jin, Y.; Wang, P.G. *Chemtech* **1999**, *2*, 23.
21. Overman, L. E.; Robinowitz, M. H.; Renhow, P. A. *J. Am. Chem. Soc*. **1995**, *117*, 1657.
22. Kappe, C. O.; Falsone, F. S. *Synlett* **1998**, 718.
23. Grover, G. J.; Dzwonczyk, S.; Normadinam, C. S.; Sleph, P.G.; Moreland, S. J. *Cardiovasc. Pharmacol*. **1995**, *28*, 289.
24. Kappe, C.O. *Tetrahedron* **1993**, *49*, 6937.
25. Ghorba, M. M.; Mohamed, Y. A.; Mohamed, S. A.; Ammar, Y. A. *Phosphorus, Sulfur, Silicon* **1996**, *108*, 249.
26. Tsuji, K.; Ishikawa, H. *Bioorg. Med .Chem. Lett*. **1994**, *4*, 1601.
27. Kidwai, M.; Mishra, A.D. *Bull. Korean Chem. Soc*. **2003**, *24*, 1038.
28. Biginelli, P. *Gazz Chim. Ital.* **1893**, *23*, 360.
29. Kappe, C. O.; Rochge, P. *J. Heterocycl. Chem*. **1989**, *26*, 55.

30. Lin, H.; Ding, J.; Chen, X.; Zhang, Z. *Molecules* **2000,** *5*, 1240.
31. Foroughifar, N.; Mobinikhaledi; Fathinejad. *Phosphorus, Sulfur, Silicon* **2003**, *178*, 495.
32. Sharaf, M. A. F.; Abdel, F. A.; Fattah, A. M.; Khalil, A. M. R. *J. Chem. Research (S)*, **1996**, 354.
33. O'Reilly, B. C.; Atwal, K.S. *Heterocycles* **1987**, *26*, 1158.
34. Shutalev, A. D.; Kishko, E. A. Sivova, N.; Kuzentsov, A.Y. *Molecules* **1989**, *3*, 100.
35. Bhuva, V. R.; Purohit, D. M.; Shah, V. H. *International Symposium on Drug Discovery and Process Research* **2003**, *130*, 80,
36. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.

