Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 667–669

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Syntheses of Novel Antimycobacterial Combinatorial Libraries of Structurally Diverse Substituted Pyrimidines by Three-Component Solid-Phase Reactions†

Arun Kumar,[a] Sudhir Sinha[b] and Prem M. S. Chauhan[a,*]

[a]*Medicinal Chemistry Division, Central Drug Research Institute, Lucknow-226001, U.P., India*
[b]*Biochemistry Division, Central Drug Research Institute, Lucknow-226001, U.P., India*

Received 25 September 2001; accepted 6 December 2001

Abstract—A new pyrimidine based scaffold has been developed by three-component solid-phase syntheses. The utility of scaffolds was demonstrated by synthesizing libraries of 80 substituted pyrimidines **12(a–p)**, **13(a–p)**, **14(a–p)**, **15(a–p)**, **16(a–p)**. Among 80 compounds screened, six compounds, **12i**, **13c**, **14d**, **14e**, **14o**, and **15d** showed in vitro activity against *Mycobacterium tuberculosis* (MABA) at a concentration of 50 and 25 μg/mL

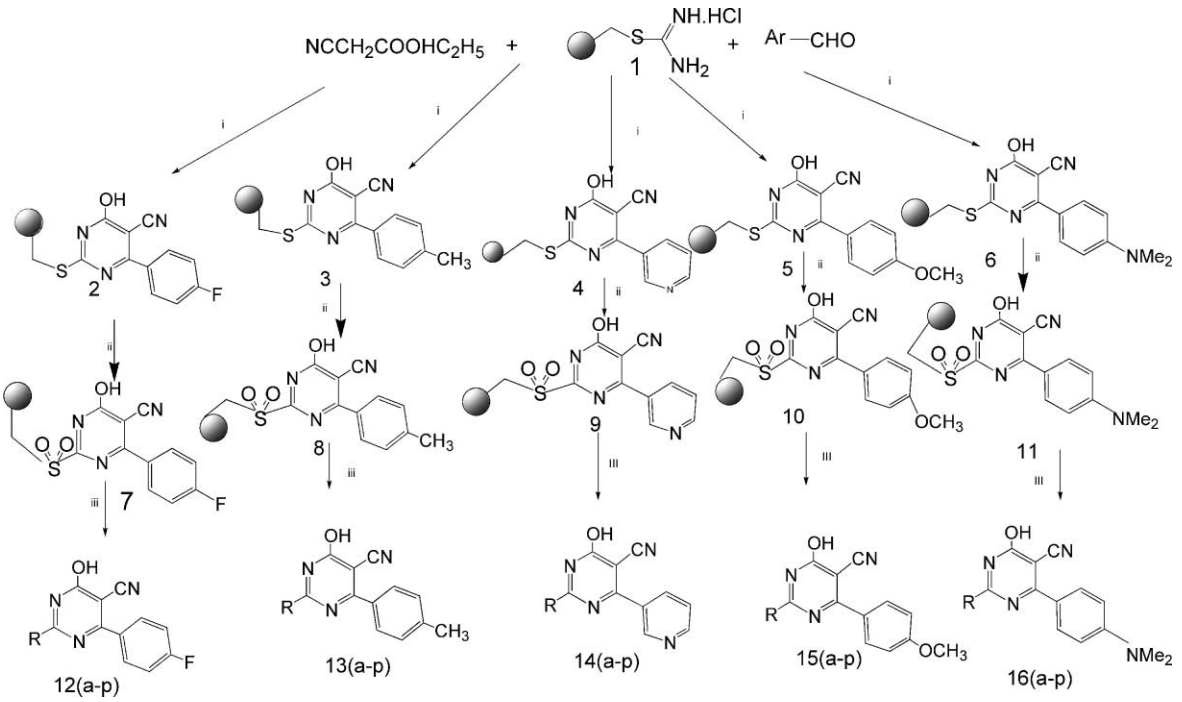
Mycobacterium tuberculosis, which causes tuberculosis, is the greatest single infectious disease cause of mortality worldwide, killing roughly two million people annually. Estimates indicate that one-third of the world population is infected with latent *M. tuberculosis*. In 1993, the World Health Organization (WHO) declared TB "a global emergency", and it is disappointing that the latest figures show that more people died from TB in 1995 than in any year in history. The statistics show a depressing eight million new cases and a death toll of three million a year, the highest from a single infectious agent. Over 95% of cases are in the developing world. In addition, about a third of the world's population harbours a dormant *M. tuberculosis* infection, representing a significant reservoir of disease for the future. The synergy between tuberculosis and the AIDS epidemic, and the surge of multidrug-resistant clinical isolates of *M. tuberculosis* have reaffirmed tuberculosis as a primary public health threat .[1–12]

In search of new antituberculosis drugs with the help of combinatorial chemistry, we have synthesized combinatorial libraries of tetrasubstituted pyrimidines as antituberculosis agents using three-component reactions, as part of our ongoing programme devoted towards the development of efficient molecularly diverse heterocycles as anti-infectious agents.[13–18] We have concentrated our attention on pyrimidine derivatives due to their broad range of useful properties such as antiallergic,[19] antitumour,[20] antipyratic[21] anti-inflammatory,[21] and antiparasitic activities.[15] Previously, we reported the solid-support synthesis of quinolones,[22] pyrimido[4,5-*d*]pyrimidines and substituted pyrimidines.[23,24] In an extension of previous studies on the generation of diversity on solid-support-bound pyrimidines we found certain limitations. These limitations in the generation of combinatorial libraries for lead optimization for pyrimidine synthesis were because of the less reactive nature of substituted groups on pyrimidines under mild conditions.[23,24] Because of this, we sought for an alternate synthesis of substituted pyrimidines. Treating support-bound thiouronium salt **1** with ethyl cyanoacetate and aromatic aldehydes yielded highly diverse substituted pyrimidines[25] due to the incorporation of aldehyde residue at position 6 and nucleophilic cleavage of the sulphones by different amines at position 2. This provided a very good centre for diversity for producing large libraries for lead identification and lead optimization. In conclusion, we report structurally diverse new pyrimidines on solid support having 2-substituted alkyl/aryl alkyl/cycloalkyl amines and 6-substituted aryl/substituted aryl. Further, the 4,5 centre can also be utilized for combinatorial purposes and large libraries can be synthesized for new lead identification in the area of tuberculosis. In the

†CDRI Communication No. 6209.

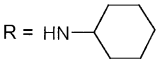
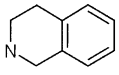
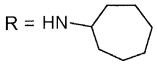
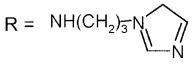
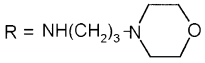
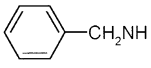
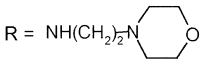
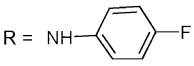
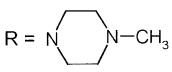
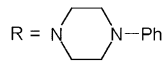
*Corresponding author. Tel.: +91-522-212411x4332; fax: +91-522-223405/223938; e-mail: prem_chauhan_2000@yahoo.com or premsc58@hotmail.com

0960-894X/02/$ - see front matter
PII: S0960-894X(01)00829-0



Scheme 1. Reagents and conditions: (i) $NCCH_2{\cdot}COOC_2H_5$, aromatic aldehyde, K_2CO_3|DMF 80°C, 30 h; (ii) MCPBA, CH_2Cl_2, rt, 18 h; (iii) amines, CH_2Cl_2, 40°C, 10 h.

Table 1.

a	$R = NH(CH_2)_3CH_3$	**j**	R = 
b	R = 	**k**	R = 
c	R = 	**l**	$R = NHCH(CH_3)(CH_2)_3NEt_2$
d	$R = NH(CH_2)_7CH_3$	**m**	R = 
e	$R = NH(CH_2)_2CH_3$	**n**	R = 
f	R = 	**o**	R = 
g	$R = NH(CH_2)_2OH$	**p**	R = 
h	R = 		
i	R = 		

present studies, we have successfully synthesized a library of 80 compounds in satisfactory yield (80–90%). Among 80 compounds screened, six compounds, **12i**, **13c**, **14d**, **14e**, **14o**, and **15d** showed in vitro activity against *M. tuberculosis*.

General Experimental Procedure

Polymer-bound thiouronium salt **1** was prepared under standard conditions[23,26] by reacting thiourea with Merrifield resin in DMF at 80 °C. Compound **1** (0.8 mmol/g) was reached with ethyl cyanoacetate (8 mmol) and different substituted aromatic aldehydes (8 mmol) and K_2CO_3 (10 mmol) in DMF at 80 °C for 24 h, shaking[27] by using an advancetech organic synthesizer 496Ω at 300 rpm. The mixture was then washed successively with DMF (30 mL, three times), CH_2Cl_2 (30 mL, three times) and methanol (30 mL, three times) to yield **2**–**6**. The resin loaded compounds **2**–**6** were oxidized with 1.2 equiv of *m*-CPBA in CH_2Cl_2 to give sulphones **7**–**11**, which were subjected to cleavage with different amines in CH_2Cl_2 at 40 °C for 10 h leading to final products **12**(**a**–**p**), **13**(**a**–**p**), **14**(**a**–**p**), **15**(**a**–**p**), and **16**(**a**–**p**) (Table 1).

After cleavage, all products were obtained in >90% purity as determined by integration of ^1H NMR signals and TLC (Scheme 1). All compounds were characterized by spectroscopic analysis.[29]

Biological Activity

All the compounds were tested against *M. tuberculosis* H37Ra cell viability (MABA) according to the method reported by Collins et al.[28] at two final concentrations, 50 and 25 μg/mL. The library of 80 compounds was tested. Among them, six compounds **12i**, **13c**, **14d**, **14e**, **14o**, and **15d** showed in vitro activity against *M. tuberculosis* at a concentration of 50 and 25 μg/mL.

Conclusion

We have identified some new anti-Mycobacterium agents. These new agents can be further utilized for lead optimization purposes and can be new leads for tuberculosis chemotherapy. We have also observed that the presence of pyridine at position 6 along with heptyl, morpholinyl and propyl amines at position 2 (**14d**, **14e**, **14o**) is very crucial for anti-Mycobacterial activity. The aryl group at position 6 along with piprazinyl, cycloheptyl and heptyl amines at position 2 (**12i**, **13c**, **15d**) is important for anti-tuberculosis activity.

Acknowledgements

Thanks to RSIC, Lucknow for providing spectroscopic and analytical data, and from one of us (A.K.) to DOD scheme for providing financial support.

References and Notes

1. Anon. *WHO Report on the Tuberculosis Epidemic*; World Health Organization: Geneva, 1997.
2. Anon. *Groups at Risk*; World Health Organization: Geneva, 1996.
3. Bloom, B. R.; Murray, C. J. L. *Science* **1992**, *257*, 1055.
4. Bloch, A. B.; Cauthen, G. M. *J. Am. Med. Assoc.* **1994**, *271*, 665.
5. Cohn, D. L.; Bustreo, F.; Raviglione, M. C. *Clin. Infect. Dis.* **1997**, *24* (Suppl. 1), S121.
6. Kenyon, T. A.; Valway, S. E.; Ihle, W. W.; Onorato, I. M.; Castro, K. G. *N. Engl. J. Med.* **1996**, *334*, 933.
7. Barnes, P. F; Bloch, A. B.; Davidson, P. T.; Snider, D. E. *N. Engl. J. Med.* **1991**, *234*, 1644.
8. Selwyn, P. A.; Hartel, D.; Lewis, V. A.; Schoen bavm, E.; Vermund, S. H.; Klein, R. S.; Walker, A. T.; Friedland, G. H. *N. Engl. J. Med.* **1989**, *320*, 545.
9. Fine, P. E. M. In *Tuberculosis: Back to the Future*; Porter, J. D. H., McAdam, K. P. W. J., Eds; John Wiley & Sons: London, 1994; p 53.
10. Saito, H.; Tomioka, H.; Sato, K.; Emori, M.; Yamane, T.; Yamashita, K.; Hosae, K.; Hidaka, T. *Antimicrob. Agents Chemother.* **1991**, *35*, 542.
11. Klemens, S. P.; Grossi, M. A.; Cynamon, M. H. *Antimicrob. Agents Chemother.* **1994**, *38*, 2245.
12. Barbachyn, M. R.; Hutchinson, D. K.; Bricknere, S. J.; Cynamon, M. H.; Kilburn, J. O.; Klemens, S. P.; Glickman, S. E.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 680.
13. Chauhan, P. M. S.; Chatterjee, R. K. *Indian J. Chem.* **1994**, *33B*, 32.
14. Shrivastava, S. K.; Chauhan, P. M. S.; Bhaduri, A. P.; Agarwal, S. K.; Singh, S. N.; Nigar, F.; Chatterjee, R. K.; Shrivastava, V. M. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2623.
15. Shrivastava, S. K.; Agarwal, A.; Chauhan, P. M. S.; Agarwal, S. K.; Bhaduri, A. P.; Singh, S. N.; Fatima, N.; Chatterjee, R. K. *J. Med. Chem.* **1999**, *42*, 1667.
16. Shrivastava, S. K.; Agarwal, A.; Chauhan, P. M. S.; Agarwal, S. K.; Bhaduri, A. P.; Singh, S. N.; Fatima, N.; Chatterjee, R. K. *Bioorg. Med. Chem.* **1999**, *7*, 1223.
17. Shrivastava, S. K.; Chauhan, P. M. S.; Bhaduri, A. P.; Fatima, N.; Chatterjee, R. K. *J. Med. Chem.* **2000**, *43*, 2275.
18. Tiwari, S.; Chauhan, P. M. S.; Bhaduri, A. P.; Singh, S. N.; Fatima, N.; Chatterjee, R. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1409.
19. Ban, M.; Taquchi, H.; Katsushima, T.; Akoki, S.; Wantanabe, A. *Bioorg. Med. Chem.* **1998**, *6*, 1057.
20. Wright, G. E.; Gombino, J. J. *J. Med. Chem.* **1984**, *27*, 181.
21. Jalander, L. F.; Longquist, J. E. *Heterocycles* **1998**, *48*, 343.
22. Shrivastava, S. K.; Haq, W.; Murthy, P. K.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1885.
23. Shrivastava, S. K.; Haq, W.; Chauhan, P. M. S. *Combin. Chem. High Throughput Screen.* **1999**, *2*, 33.
24. Shrivastava, S. K.; Haq, W.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 965.
25. Chauhan, P. M. S.; Kumar, A. *Combin. Chem. High Throughput Screen*, in press.
26. Obrecht, D.; Abrecht, C.; Grider, A.; Villalgordo, J. M. *Helv. Chem. Acta* **1997**, *80*, 65.
27. Hussain, S. M.; Barbary, A. A.; Mansour, S. A. *J. Heterocyc. Chem.* **1985**, *22*, 169.
28. Collins, L. A.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **1997**, *45*, 1004.
29. **2**. IR: 3338, 2918, 2214, 1643, 1386 cm^{-1}. **7**. IR: 3398, 3026, 2927, 2224, 1599, 1499, 1254, 1146 cm^{-1}. **12i**. IR: 3437, 3060, 2919, 2210, 1597, 1241 cm^{-1}. FAB MS: 375 (M+); ^1H NMR (200 MHz, $CDCl_3$) δ 8.05 (d, 2H, $J=10$ Hz), 7.39–7.26 (m, 4H), 6.95–6.88 (m, 5H), 3.34–3.22 (m, 8H). **3**. IR: 3394, 3035, 2925, 2210, 1529, 1268, 1003 cm^{-1}. **8**. IR: 3392, 3023, 2916, 2213, 1924, 1540, 1153, 1003 cm^{-1}. **13i**. IR: 3422, 2920, 2816, 2196, 1598 cm^{-1}. M^+ 371. ^1H NMR ($CDCl_3$) δ 7.91 (d, 1H, $J=10$ Hz), 7.28–7.24 (m, 4H), 6.95–6.86 (m, 5H), 3.37–3.21 (m, 8H), 2.41 (s, 3H). **4**. IR: 3427, 2210, 1597, 1352, 1087 cm^{-1}. **9c**. IR: 3445, 2990, 2197, 1599, 1357, 1015 cm^{-1}. **14l**. IR: 45, 2990, 2816, 2197, 1599, 1350, 1015 cm^{-1}. M+ 358. ^1H NMR δ 9.1 (d, $J=1.8$ Hz), 8.72 (dd, $J=1.6$, 4.0 Hz), 8.31 (d, 1H, $J=8.2$ Hz), 7.43–7.41 (m, 2H), 6.94–6.87 (m, 5H). **5**. IR: 3351, 2208, 1813, 1759, 1631, 1350, 1091 cm^{-1}. **10**. IR: 3411, 3023, 2920, 2216, 1599, 1364, 1248, 1172, 1023 cm^{-1}. **15i**. IR: 3424, 2838, 2198, 1599, 1375, 1209, 1024 cm^{-1}. M+387. ^1H NMR δ 8.05 (d, 1H, $J=10$ Hz), 7.32–7.24 (m, 4H), 7.01–6.88 (m, 5H), 3.87 (s, 3H), 3.34–3.29 (m, 8H). **6**. IR: 3493, 2924, 2210, 1597, 1352, 1016 cm^{-1}. **11**. IR: 3429, 2927, 2206, 1598, 1352, 1173, 1021 cm^{-1}. **16i**. IR: 3431, 2927, 2206, 1598, 1352, 1173, 1021 cm^{-1}. M^+ 400. ^1H NMR δ 8.0 (d, 1H, $J=10$ Hz), 7.36–7.26 (m, 4H), 6.99–6.85 (m, 5H), 3.54–3.38 (m, 8H).