HETEROCYCLES, Vol. 57, No. 12, 2002,pp. 2383 - 2391, Received, 6th August, 2002

SYNTHESIS OF 4-(1,4-DIARYL-2*H*-CYCLOPENT[*d*]PYRIDAZIN-2-YL)-BENZENESULFONAMIDES

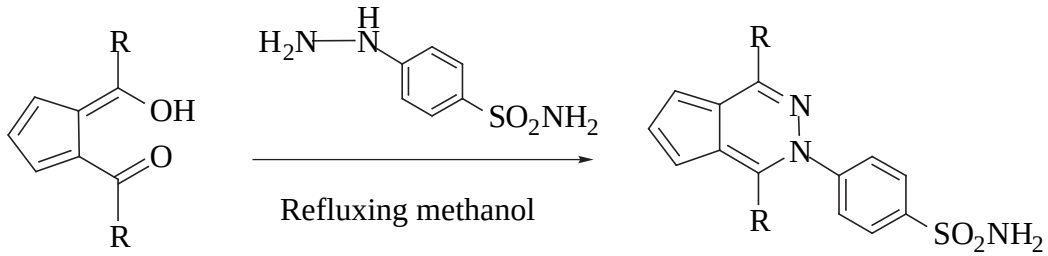
Mark Blankenbuehler* and Sean Parkin[†]

* Morehead State University, Department of Physical Sciences, Morehead, Kentucky, 40351 USA. † University of Kentucky, Department of Chemistry, Lexington, Kentucky, 40506 USA.

Abstract - The condensation of cyclopentadienyl-derived γ-diketones and arylhydrazines was utilized to synthesize 4-(1,4-diphenyl-2*H*-cyclopent[*d*]-pyridazin-2-yl)benzenesulfonamide and 4-(1,4-di-(4-methylphenyl)-2*H*-cyclo-pent[*d*]pyridazin-2-yl)benzenesulfonamide in better than 80% yield. The crystal structures of the precursor hydroxyfulvene, {(5*Z*)-5-[hydroxy(4-methylphenyl)-methylene]cyclopenta-1,3-dien-1-yl}(4-methylphenyl)methanone, and the derived pyridazine 4-(1,4-diphenyl-2*H*-cyclopent[*d*]pyridazin-2-yl)benzene-sulfonamide, were also obtained.

The sulfonamide functional group has exhibited its importance by its presence in a large variety of pharmaceuticals covering a wide range of biological activities. Potential pharmaceuticals that are designed to target the eicosanoid pathway of synthesis are of current interest. Examples of eicosanoids are prostaglandins, thromboxanes, and prostacyclins, which are responsible for pain and inflammation. Selectivity of isoenzymes is of particular importance for these potential pharmaceuticals. Cyclooxygenase (COX)–2 is the isoenzyme many of these potential pharmaceuticals are designed to inhibit. COX-2 is found in mast cells and is the key enzyme that converts arachidonic acid into prostaglandins. Failure of specificity for the COX-2 enzyme can lead to possible gastrointestinal toxic effects due to the inhibition of COX-1.[1-6] Celebrex, a diarylpyrazole, is one example of a diarylpyrazolebenzenesulfonamide that is currently in use and currently under study.[4,7-11] Expanding the number of available benzenesulfonamides for testing to cyclopenta[*d*]pyridazines similar to existing selective COX-2 inhibitors could lead to additional effective pharmaceuticals. The condensation reaction of γ– and β – diketones has been known for some time although the chemistry related to cyclopenta[*d*]pyridazine remains relatively unexplored. Reports by Anderson *et al.*[12-14] demonstrate the ring closure with hydrazine and simple arylhydrazines. The current study seeks to expand the variety of hydrazines used in the ring closure reaction, specifically 4-hydrazinobenzenesulfonamide (see Scheme 1).

Scheme 1. Synthesis of 4-(1,4-diaryl-2*H*-cyclopent[*d*]pyridazin-2-yl)benzenesulfonamides.



2, 3: R = Ph, 4-MePh

4, 5: R = Ph, 4-MePh

Although historically the synthesis of 4-hydrazinobenzenesulfonamide•HCl, (**1**), has been through the diazotination of the corresponding amine and subsequent reduction *via* stannous chloride,[15] another route *via* the reaction of hydrazine with 4-chlorobenzenesulfonamide gave better and more consistent yields. The stable 4-hydrazinobenzenesulfonamide•HCl salt must be neutralized with hydroxide to form the free base (**1a**) before the ring closure will take place. The synthesis of precursor {(5*Z*)-5-[hydroxy(phenyl)methylene]cyclopenta-1,3-dien-1-yl}(phenyl)methanone (**2**), and {(5*Z*)-5-[hydroxy(4-methylphenyl)methylene]cyclopenta-1,3-dien-1-yl}(4-methylphenyl)methanone (**3**), have been previously reported by Linn and Sharkey.[16] The method of Linn and Sharkey using lithium cyclopentadienide and the corresponding acyl halide is convenient and yields of 75-85% are typically achieved although previously reported yields were about 35%. Traditional solvent combinations for the ring closure such as ethanol or ethanol/water were unsuccessful. The mixture of 4-hydrazinobenzenesulfonamide and compound (**2**) or (**3**) in refluxing methanol gave the product sulfonamide (**4**) or (**5**), respectively, in nearly quantitative yield. Full characterization of **3**, **4** and **5** as well as crystal structures for (**3**) (see Figure 1) and (**4**) (see Figure 2) were obtained. Both exhibit the expected planar structures associated with 6-electron cyclopentadienyl, compound (**3**), or 10-electron bicyclic aromatic systems, compound (**4**) (see Table 2).

Discussion: Full analysis was performed on all compounds. Compound (**3**) shows a downfield singlet for the enol hydrogen at 18.3 ppm as expected. Compounds (**4**) and (**5**) both show complex aromatic regions in the ^{1}H NMR spectrum as expected because of the asymmetry. *Para* splitting was evident and resolved in both cases. ^{13}C NMR spectra were also obtained showing individual peaks for each chemically inequivalent carbon. Infrared spectra showed the expected N-H and S=O stretches in the 3400-3600 cm^{-1} and 1350-1000 cm^{-1} regions respectively. Melting points were very high and neither **4** or **5** showed any observable change under 260°C. MS data showed the appropriate molecular ion and fragmentation patterns. The crystal structure of **3** shows a nearly planar arrangement between the cyclopentadienyl ring and the oxygen atoms with torsion angles of -11.0 and 5.0 degrees.

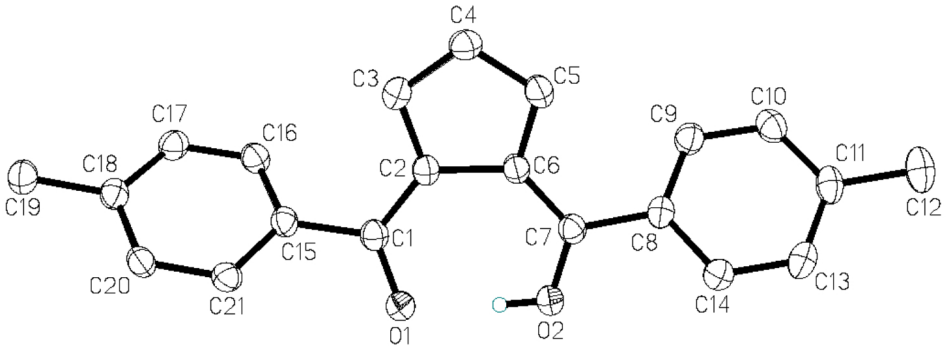


Figure 1. Thermal ellipsoid plot of the X-Ray structure of **3** showing 50% probability ellipsoids. Hydrogens have been omitted for clarity.

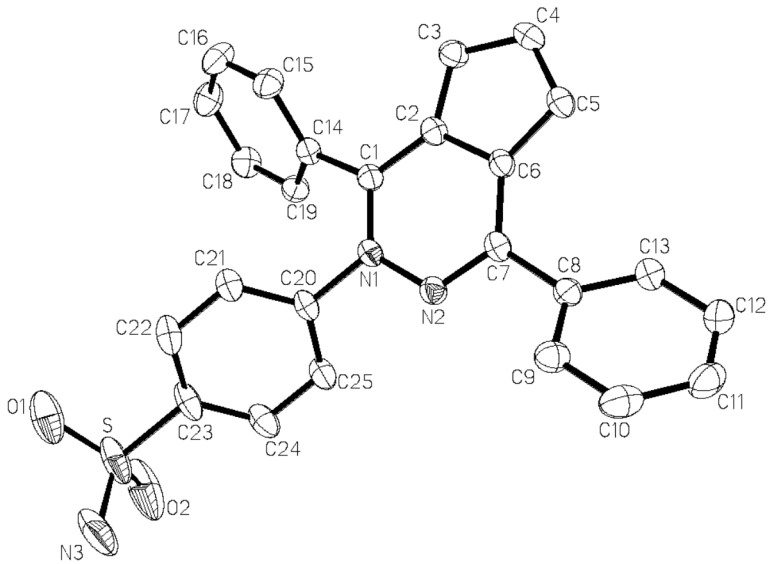


Figure 2. Thermal ellipsoid plot of the X-Ray structure of **4** showing 50% probability ellipsoids. Hydrogens have been omitted for clarity.

The phenyl groups are twisted out of the plane of the cyclopentadienyl ring and nearly perpendicular to each other. Torsion angles for the aromatic rings are 51.3 and -38.6 degrees. Carbon to oxygen bond lengths are 1.276 and 1.288 Å indicating a symmetric structure. The crystal structure of **4** indicates a planar structure with torsion angles in the pyridazine ring of -178.1, 0.9, and 0.1 degrees. The aromatic rings are twisted out of the plane between -37.4 and -56.5 degrees. The N-substituted aromatic ring is twisted -50.6 degrees out of the plane. The N1 nitrogen bond angles are 125.3, 122.4 and 112.2 degrees, and torsion angles of -178.1 and -7.0 degrees show a nearly trigonal planar structure. Bond lengths in the remaining bicyclic structure indicate a

conjugated ring system with bonds C1-C2, C3-C4, C5-C6, and C7-N2 averaging 1.371 Å and is 0.031 Å shorter than the average C2-C3, C4-C5, C6-C7 and N1-C1 bond distance (1.402 Å). Carbon to nitrogen distances, 1.366 and 1.322 Å are similar to pyrazole, 1.35 Å, and pyridazine systems.

Table 1. Crystal Data and Structure Refinement for Compound (**3**) and (**4**).

Compound	**3**	**4**
Empirical formula	$C_{21}\ H_{18}\ O_2$	$C_{25.70}\ H_{20.40}\ Cl_{1.40}\ N_3\ O_2\ S$
Formula weight	302.35	484.94
Crystal System, space group	Monoclinic, P 2_1/n	Triclinic, P -1
Unit Cell Dimensions (Å, deg)	a = 10.0970(10) α = 90 b = 7.3520(10) β = 91.279(10) c = 20.658(2) γ = 90	a = 9.5480(2) α = 73.4290(14) b = 10.3630(3) β = 73.6780(14) c = 14.3720(4) γ = 63.3060(13)
Volume ($Å^3$)	1533.1(3)	1198.15(5)
Z, Calculated density (Mg/m^3)	4, 1.310	2, 1.344
Absorption coefficient (mm^{-1})	0.083	0.319
F(000)	640	503
Crystal size (mm^3)	0.50 x 0.50 x 0.28	0.30 x 0.25 x 0.20
2θ range (deg)	1.97 to 27.47	2.24 to 27.49
Limiting indices	-13≤h≤13 -9≤k≤9 -26≤l≤26	-12≤h≤12 -13≤k≤13 -18≤l≤18
Reflections collected / unique	12571 / 3509 [R(int) = 0.0402]	10909 / 5495 [R(int) = 0.0280]
Completeness to theta = 27.47	99.9%	99.8%
Max. and min. transmission	0.9772 and 0.9597	0.9389 and 0.9103
Data / restraints / parameters	3509 / 0 / 212	5495 / 0 / 307
Goodness-of-fit on F^2	1.048	1.045
Final R indices [I>2sigma(I)]	R_1 = 0.0493, wR_2 = 0.1231	R_1 = 0.0717, wR_2 = 0.2140
R indices (all data)	R_1 = 0.0707, wR_2 = 0.1354	R_1 = 0.0936, wR_2 = 0.2293
Δ(ρ)max and min	.281 and -.274 e $Å^{-3}$	1.036 and -.684 e $Å^{-3}$

Table 2. Selected Bond Lengths (Å), Bond Angles (º) and Torsion Angles (º) for Compounds (**3**) and (**4**).

3		**4**	
Length		**Length**	
O(1)-C(1)	1.2762(18)	N(1)-C(1)	1.366(3)

O(2)-C(7)	1.2881(18)	N(2)-C(7)	1.322(3)
		N(1)-C(20)	1.442(3)
		N(1)-N(2)	1.378(3)
C(1)-C(2)	1.415(2)	C(1)-C(2)	1.374(3)
C(6)-C(7)	1.408(2)	C(6)-C(7)	1.414(4)
C(2)-C(6)	1.4645(19)	C(2)-C(6)	1.458(3)
C(2)-C(3)	1.409(2)	C(2)-C(3)	1.417(4)
C(3)-C(4)	1.390(2)	C(3)-C(4)	1.389(4)
C(4)-C(5)	1.392(2)	C(4)-C(5)	1.411(4)
C(5)-C(6)	1.413(2)	C(5)-C(6)	1.397(3)
Angle		**Angle**	
O(1)-C(1)-C(2)	123.29(13)	N(1)-C(1)-C(2)	117.3(2)
C(1)-C(2)-C(6)	128.85(13)	C(1)-C(2)-C(6)	119.8(2)
O(2)-C(7)-C(6)	123.22(13)	N(2)-C(7)-C(6)	122.7(2)
C(7)-C(6)-C(2)	128.77(13)	C(7)-C(6)-C(2)	116.9(2)
C(4)-C(3)-C(2)	109.60(13)	C(4)-C(3)-C(2)	107.2(2)
C(3)-C(2)-C(6)	106.34(13)	C(3)-C(2)-C(6)	107.5(2)
C(3)-C(4)-C(5)	108.36(13)	C(3)-C(4)-C(5)	110.4(2)
		N(2)-N(1)-C(20)	112.2(2)
		C(1)-N(1)-C(20)	122.4(2)
		C(7)-N(2)-N(1)	117.8(2)
Torsion Angle		**Torsion Angle**	
C(2)-C(6)-C(7)-O(2)	-11.0(2)	C(2)-C(6)-C(7)-N(2)	-3.8(4)
O(1)-C(1)-C(2)-C(6)	5.0(2)	N(1)-C(1)-C(2)-C(6)	0.9(4)
C(2)-C(1)-C(15)-C(16)	51.3(2)	C(2)-C(1)-C(14)-C(15)	-56.5(3)
C(6)-C(7)-C(8)-C(9)	-38.6(2)	C(6)-C(7)-C(8)-C(13)	-37.4(4)
		C(20)-N(1)-N(2)-C(7)	-178.1(2)
		C(1)-N(1)-N(2)-C(7)	4.7(4)
		C(20)-N(1)-C(1)-C(14)	-7.0(4)
		N(1)-N(2)-C(7)-C(6)	0.1(4)
		N(2)-N(1)-C(20)-C(25)	-50.6(3)

In conclusion, the benzenesulfonamides (**4**) and (**5**) have been synthesized in good overall yield from the reaction of a suitable gamma diketone and a sulfonamide substituted arylhydrazine.

EXPERIMENTAL

All air-sensitive reactions were carried out using standard Schlenk techniques under a nitrogen atmosphere unless otherwise noted. Dry tetrahydrofuran, benzoyl chloride and *p*-toluoyl chloride (Aldrich) were purchased from Aldrich and used as received. Hydrazine was 65% by weight with water. $CDCl_3$, acetone-d_6 and DMSO-d_6 were purchased from Cambridge Isotopes and used without further purification. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 200 spectrometer. IR spectra were obtained on a Mattson Galaxy Series FTIR 3000. Melting points are uncorrected. Elemental analyses were performed at the University of Illinois, Urbana. MS spectral data were collected at the University of Kentucky Mass Spectrometry Center. Crystal structures were obtained by Sean Parkin at the University of Kentucky X-Ray crystallography facility using a Nonius KappaCCD at 173 K and Molybdenum Kα radiation at 0.71073 Å. A semi-empirical absorption correction based on equivalent reflections was applied to the data.

4-hydrazinobenzenesulfonamide•HCl (1)

Procedure adapted from personal communication with Tom Archibald, Aerojet-General Corporation: Patent reference.[17] 4-Chlorobenzenesulfonamide (2.05 g, 0.0107 mol) was added to a round-bottom flask. Hydrazine (0.35 mL, 0.011 mol) was added with 15 mL of water and the mixture refluxed for 30-40 h. The reaction was cooled to 0-5°C and the free base product precipitated. The solid was washed with cold water and cold methanol to remove excess hydrazine. Fresh methanol was added and concentrated HCl was added to the methanol slurry until the pH was less than 2.5. The mixture was stirred and heated to reflux. The solution was again cooled to -5 to 5 °C and the HCl salt crystallized. The product salt was filtered and washed with a minimum of cold methanol. Compound (**1**) was recovered (1.27 g, 53.2%) as an off-white solid. Yields of 50-60% were typical.

4-Hydrazinobenzenesulfonamide (1a)

Compound (**1**) (5.03 g, 22.5 mmol) was dissolved in a minimum amount of water (approx. 50 mL). The pH was adjusted to 8 with 2 M sodium hydroxide and 2 M HCl, if necessary, and a white solid precipitated. The mixture was vacuum-filtered and the resulting shiny, pearl-white solid was rinsed with ice-cold distilled water. The product was dried in air for 24 h and **1a** was recovered (2.77 g, 65.8%). The melting point was 158-159 ºC.

Hydroxyfulvene derivatives (2, 3)

General procedure: Freshly cracked cyclopentadiene (5.0 mL, 62 mmol) was added to a Schlenk flask containing approximately 100 mL dry ether at 0°C. *n*-Butyllithium (24 mL, 64 mmol) was added slowly and a white suspension formed. *p*-Toluoyl chloride (5.3 mL, 40 mmol) or benzoyl chloride (4.8 mL, 40 mmol) was added slowly *via* syringe. The solution was allowed to warm and stirred at rt for at least 45 min. A 10% acetic acid solution (100 mL) was added to quench the reaction and the mixture was extracted with ethyl ether. The

organic layer was washed with water three times and dried with magnesium sulfate. The yellow solution was filtered and the ether removed on a rotary evaporator. Yields were consistently greater than 75%. Crystals for X-Ray diffraction were grown by slow evaporation from a saturated acetone solution.

{(5*Z*)-5-[Hydroxy(4-methylphenyl)methylene]cyclopenta-1,3-dien-1-yl}(4-methylphenyl)methanone (3)

mp 147-148°C (lit.,[16]148-149 °C). ^{1}H-NMR (ppm, acetone-d_6) : 18.60 (s, 1H, OH), 7.73 (d, J_{HH} = 8.0 Hz, 4H, H_{arom}), 7.39 (d, J_{HH} = 8.0 Hz, 4H, H_{arom}), 7.29 (d, J_{HH} = 4.0 Hz, 2H, Cp), 6.52 (t, J_{HH} = 4.0 Hz, 1H, Cp), 2.45 (s, 6H, CH_3). ^{13}C-NMR (ppm, acetone-d_6) : 193.1 (CO), 142.1 (Cp), 141.0 (Cp), 134.7 (*i*-Ph), 129.7 (*o,m*-Ph), 128.8 (*o,m*-Ph), 124.0 (*p*-Ph), 105.3 (Cp), 20.5 (CH_3). MS(EI): 302 (M^+, 100%), 210 (M^+ - C_7H_7, 37%), 119 (M^+ - 2(C_7H_7), 50%), 91 ($C_7H_7^+$, 37%). IR (cm^{-1}, thin film): 3420 (br, OH), 1637 (br, CO). Anal. Calcd for $C_{21}H_{18}O_2$ • 0.5 $C_4H_{10}O$: C, 81.40; H, 6.70. Found: C, 81.15; H, 6.00.

Benzenesulfonamide derivatives (4,5)

Compound (**2**) or (**3**) (0.012 mol) and compound (**1a**) (2.81 g, 0.015 mol) were added to 25-50 mL of reagent grade methanol and refluxed overnight. After several hours a yellow solid precipitates. The reaction mixture was cooled to rt and the solution filtered. The yellow, crystalline material was washed with small portions of ice cold methanol. Typical recovered yields were 80 - 90%. Crystals for X-Ray diffraction were grown by slow diffusion of ether into a dichloromethane solution *via* layering or slow vapor diffusion.

4-(1,4-Diphenyl-2*H*-cyclopent[*d*]pyridazin-2-yl)benzenesulfonamide (4)

mp >260°C. ^{1}H-NMR (ppm, DMSO-d_6) : 8.12 (m, 2H, H_{arom}), 7.88 (d, J_{HH} = 8.8 Hz, 2H, H_{arom}), 7.70 (d, J_{HH} = 8.8 Hz, 2H, H_{arom}), 7.56 (m, 4H, H_{arom}), 7.43 (m, 4H, H_{arom}), 7.04 (dd, J_{HH} = 3.2 Hz, J_{HH} = 1.4 Hz, 1H, Cp), 6.69 (d, J_{HH} = 3.2 Hz, 2H, Cp). ^{13}C-NMR (ppm, DMSO-d_6) : 149.0 (CN), 147.1 (CN), 145.7 (Cp), 143.8 (Cp), 137.0 (*i*-Ph), 133.3 (*i*-Ph), 132.7 (*i*-Ph), 130.3 (*o,m*-Ph), 129.8 (*o,m*-Ph), 129.1 (*o,m*-Ph), 128.9 (*o,m*-Ph), 128.8 (*o,m*-Ph), 128.6 (*o,m*-Ph), 126.4 (*p*-Ph), 124.4 (*p*-Ph), 119.1 (*p*-Ph), 110.9 (Cp), 108.6 (Cp), 96.9 (Cp). MS(EI):425 (M^+, 100%), 344 (M^+ - SO_2NH_2, 7%), 241 (M^+ - $N_2C_6H_4SO_2NH_2$, 24%). IR (cm^{-1}, thin film): 3682 (NH), 1602 (CN), 1327, 1165 (SO_2). Anal. Calcd for $C_{25}H_{19}N_3O_2S$ • CH_4O: C, 68.25; H, 5.07; N, 9.18. Found: C, 67.93; H, 4.41; N, 9.43.

4-(1,4-Di-(4-methylphenyl)-2*H*-cyclopent[*d*]pyridazin-2-yl)benzenesulfonamide (5)

mp >260°C. ^{1}H-NMR (ppm, DMSO-d_6) : 8.00 (d, J_{HH}=8.2 Hz, 2H, H_{arom}), 7.88 (d, J_{HH}=8.4 Hz, 2H, H_{arom}), 7.68 (d, J_{HH}=8.4 Hz, 2H, H_{arom}), 7.44 (d, J_{HH}=8.2 Hz, 2H, H_{arom}), 7.26 (dd, J_{HH}=8.4 Hz, 2H, H_{arom}), 7.00 (d, J_{HH}=3.9 Hz, 1H, Cp), 6.68 (d, J_{HH}=4.1 Hz, 2H, Cp), 2.43 (s, 3H, CH_3), 2.36 (s, 3H, CH_3). ^{13}C-NMR (ppm, DMSO-d_6) : 148.9(CN), 147.3(CN), 145.7(*i*-Ph), 143.7(Cp), 139.5(Cp), 134.3(*o,m*-Ph), 133.0(*o,m*-Ph), 130.2(*o,m*-Ph), 129.8(*o,m*-Ph), 129.4(*o,m*-Ph), 128.8(*o,m*-Ph), 128.6(*o,m*-Ph), 126.5(*p*-Ph), 124.4(*p*-Ph), 119.0(*p*-Ph),

110.9(Cp), 108.6(Cp), 21.3(CH_3). MS(EI): 453 (M^+, 100%). IR (cm^{-1}, thin film): 3403 (NH), 1574 (CN), 1336, 1156 (SO_2). Anal. Calcd for $C_{27}H_{23}N_3O_2S$: C, 71.50; H, 5.11; N, 9.26. Found: C, 71.48; H, 5.09; N, 9.24.

ACKNOWLEDGEMENT

Financial support by the NSF-KY EPSCoR Program and Morehead State University Research and Creative Productions Committee. Additional informative communication with Tom Archibald at Aerojet General Corporation was invaluable.

* Address correspondence to:

Dr. Mark Blankenbuehler , Morehead State University, 425F Lappin Hall, Morehead, KY 40351. USA.

Phone: 606-783-2915

Fax: 606-783-5002

E-Mail: m.blanken@moreheadstate.edu

REFERENCES

1. K. Nagarajan, V. Pattabhi and G. F. Fabiola, *Bioorganic & Medicinal Chemistry,* 1998, **6**, 2337.
2. A. S. Kalgutkar and L. J. Marnett, *NPS,* 1999, **26**, 465.
3. C. J. Hawkey, *Lancet,* 1999, **353**, 307.
4. P. W. Collins, J. Carter, S. R. Bertenshaw, J. J. Talley and T. D. Penning, *J. Med. Chem.,* 1997, **40**, 1347.
5. J. Ryn and M. Pairet, *Inflamm. Res.,* 1998, **47**, S93.
6. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, P. C. Isakson, L. F. Lee, J. W. Malecha, J. M. Miyashiro, T. D. Penning, R. S. Rogers, D. J. Rogier, S.A. Yu, G.D. Anderson, E. G. Burton, N. J. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A.W. Veehuizen and Y. Y. Zhang, *Actualities de Chimie Therapeutique,* 1999, **25**, 123.
7. T. Ochi, T. Tojo, N. Konishi, K. Nakamura and K. Tsuji, *Chem. Pharm. Bull.,* 1997, **45**, 987.
8. T. Ochi, K. Jobo-Magari, A. Yonezawa, K. Matsumori and T. Fujii, *Euro. J. of Pharmacology,* 1999, **365**, 259.
9. Z.-N. Mei, Z. Shi, X.-H. Wang and S.-D. Luo, *Zhongguo Yiyao Gongye Zazhi,* 2000, **31**, 433.
10. A. G. Habeeb, P. N. P. Rao and E. E. Knaus, *J. Med. Chem.,* 2001, **44**, 3039.
11. Y. Guo, Y. Xiao, Z. Guo and G. Cheng, *Yaoxue Xuebao,* 2001, **36**, 735.
12. A. G. Anderson, *J. Am. Chem. Soc.,* 1969, **91**, 924.
13. A. G. Anderson, L. D. Grina and D. M. Forkey, *J. Org. Chem.,* 1972, **37**, 3499.
14. A. G. Anderson and R. P. Ko, *J. Org. Chem.,* 1984, **49**, 4769.
15. I. M. Hunsburger, E. R. Shaw, J. Fugger, R. Ketcham and D. Lednicer, *J. Org. Chem.,* 1956, **21**, 394.
16. W. J. Linn and W. H. Sharkey, *J. Am. Chem. Soc.,* 1957, **79**, 4970.

17. T. G. Archibald and J. C. Barnard, In *Eur. Pat. Appl.*, 1999, p. 11.