Diversity-Oriented Synthesis

Synthetic Strategy toward Skeletal Diversity via Solid-Supported, Otherwise Unstable Reactive Intermediates**

*Steven J. Taylor, Alexander M. Taylor, and Stuart L. Schreiber**

Herein we report a new diversity-oriented synthetic pathway to skeletally diverse alkaloid-like compounds from simple, readily available starting materials. The synthetic strategy involves the generation and isolation of reactive, otherwise unstable dihydropyridines and dihydroisoquinolines on a solid support. A variety of reactions can be performed with the enamine double bond present in the isolated reactive intermediates, thus leading to skeletally diverse alkaloid-like products.

Small molecules used in chemical genetic[1] screens can be synthesized with guidance from compounds known to have biological activity[2a] or with the desire to distribute the products in chemical descriptor space. In the latter case, it may be advantageous to maximize the representation of different functional groups and conformations in a screen, since in most cases the nature of the small-molecule–target interaction can not be foreseen.[2b,c] Whereas complex molecules with many distinct appendages can be synthesized efficiently by using complexity-generating reactions[3] and appending processes,[4] there have been limited examples of synthetic pathways that yield products with a high degree of skeletal diversity.[5] Herein we report a three-step diversity-oriented synthetic pathway (Figure 1) based on reactive dihydroisoquinoline and dihydropyridine intermediates, which undergo a variety of transformations to generate skeletally diverse alkaloid-like compounds.

We anticipated that the enamine moiety contained in dihydropyridines and dihydroisoquinolines could be targeted selectively to undergo a variety of transformations known to

[*] Dr. S. J. Taylor, A. M. Taylor, Prof. S. L. Schreiber
Howard Hughes Medical Institute
Department of Chemistry and Chemical Biology, and ICCB
Harvard University
12 Oxford Street, Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-0751
E-mail: stuart_schreiber@harvard.edu

[**] We are especially grateful to John Tallarico and Max Narovlyansky at ICCB for the donation of synthesis resin. S.J.T. was supported by a postdoctoral fellowship (DRG-1735-02) of the Damon Runyon Cancer Research Foundation. A.M.T. was supported by a training grant managed by the Molecular, Cellular, and Chemical Biology Program. S.L.S. is an investigator at the Howard Hughes Medical Institute in the Department of Chemistry and Chemical Biology. We thank the National Institute for General Medical Sciences for their support of this research, the National Cancer Institute (NCI), Merck KGaA, Merck & Co., and the Keck Foundation for their support of ICCB, and the NCI for their support of the Initiative for Chemical Genetics.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200353466

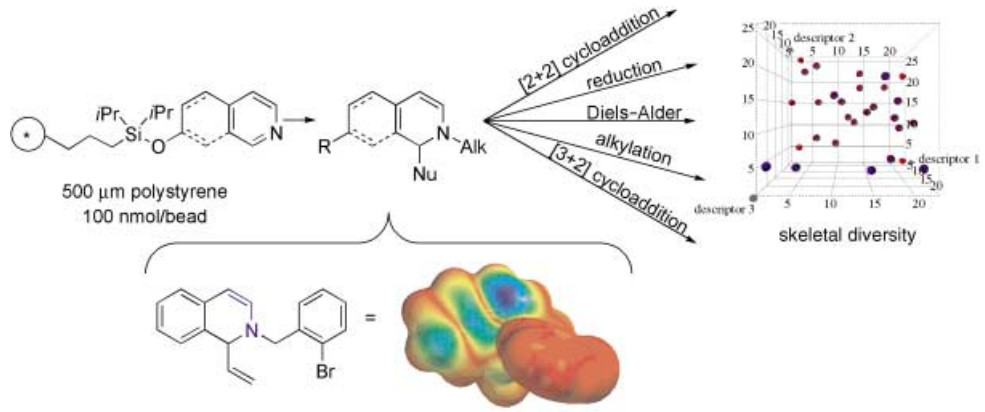


Figure 1. Outline of the diversity-oriented synthetic strategy. A three-step reaction sequence involving isolatable enamine intermediates allows the generation of skeletally diverse alkaloid-like compounds. An overlay of the calculated electron-density map (blue represents high electron density) onto the MM2 minimized geometry of the dihydroisoquinoline intermediate shows the electron-rich enamine double bond that is used as a handle for diversification reactions. Alk = alkyl, Nu = nucleophile.

occur with electron-rich olefins.[6] To test this hypothesis, we generated dihydropyridine and dihydroisoquinoline intermediates on macrobeads (silicon-functionalized 500–600-µm polystyrene components of a one-bead/one-stock solution technology platform).[7] By standard procedures,[8] 7-hydroxyisoquinoline was attached covalently to the macrobeads to generate the heterocycle **2** (Figure 2). Subsequent alkylation

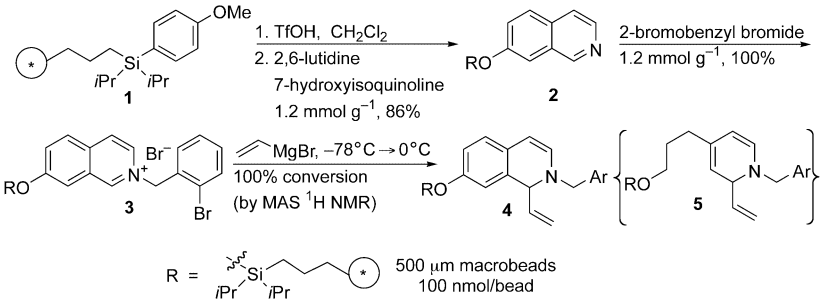


Figure 2. Solid-phase synthesis of the dihydroisoquinoline and dihydropyridine reactive intermediates. Yields based upon weight of compound after cleavage from the solid support with HF·pyridine. Conversion based upon magic angle spinning ^{1}H NMR spectroscopic analysis and comparison with the corresponding enamines synthesized in solution. Tf = trifluoromethanesulfonyl.

of **2** with 2-bromobenzyl bromide provided the iminium salt **3** quantitatively. The addition of vinylmagnesium bromide to **3** then provided the dihydroisoquinoline **4** with 100% conversion based upon magic angle spinning (MAS) ^{1}H NMR spectroscopy. In an analogous set of transformations, the corresponding dihydropyridine **5** was generated in similar yield and purity from 3-(4-pyridyl)propan-1-ol (see Supporting Information for details).[9]

Dihydropyridines and dihydroisoquinolines have been reported to be unstable even when stored under seemingly inert conditions.[10] Our initial experiments with test compounds similar to **4** in solution mirrored published results, and we observed extensive degradation of the compounds. However, attached to the solid support the dihydropyridines and dihydroisoquinolines proved to be more stable. They showed no degradation even after 1 month at room temperature. A comparison experiment validated these observations (Figure 3). When the dihydroisoquinoline analogous to **4** (derived from isoquinoline, 2-bromobenzyl bromide, and vinylmagnesium bromide) was stored frozen in benzene at 0 °C or neat at 0 °C, impurities were observed immediately and increased in quantity over time, whereas **4** (the dihydroisoquinoline on solid support) showed no degradation after 1 month of storage at room temperature. The integrity of this enamine is critical to the synthesis of more complex skeletons, since it serves as a reactive handle for cycloadditions, alkylations, and reductions.

With the dihydropyridine **5** and dihydroisoquinoline **4** in hand we then examined a variety of reactions known to occur with similar functional groups in solution.[11] Selective reduction of the enamine occurred when either **4** or **5** was exposed to $Na(CN)BH_3$ in CF_3CH_2OH/CH_2Cl_2, thus providing the corresponding reduced compounds **6** and **11a/b** (Table 1, entries 1 and 6).[12] The treatment of **4** with benzohydroximinoyl chloride provided the 6,5-fused cycloadduct **7** as a single diastereomer (Table 1, entry 2).[13] When treated with an electron-deficient azide, **4** and **5** underwent [3+2] cycloaddition followed by loss of nitrogen to yield compounds **8** and **12** (Table 1, entries 3 and 7).[14] When the enamines were exposed to dimethyl acetylenedicarboxylate (DMDA) they underwent [2+2] cycloaddition followed by ring expansion to generate the eight-membered heterocycles **9** and **13** (Table 1, entries 4 and 8).[15] The conjugated amide **10** was produced upon exposure of **4** to 4-fluorophenyl isocyanate (Table 1, entry 5).[16] The electron-rich diene **5** underwent a Diels–Alder reaction with *N*-benzylmaleimide to provide the bridged bicyclic compound **14** as a single diastereomer (Table 1, entry 9).[17]

For a qualitative assessment of the overall topography of the molecules listed in Table 1 and Figure 2, a low-energy conformation was calculated for each compound.[18] An overlay of the isoquinoline-derived minimized skeletons at

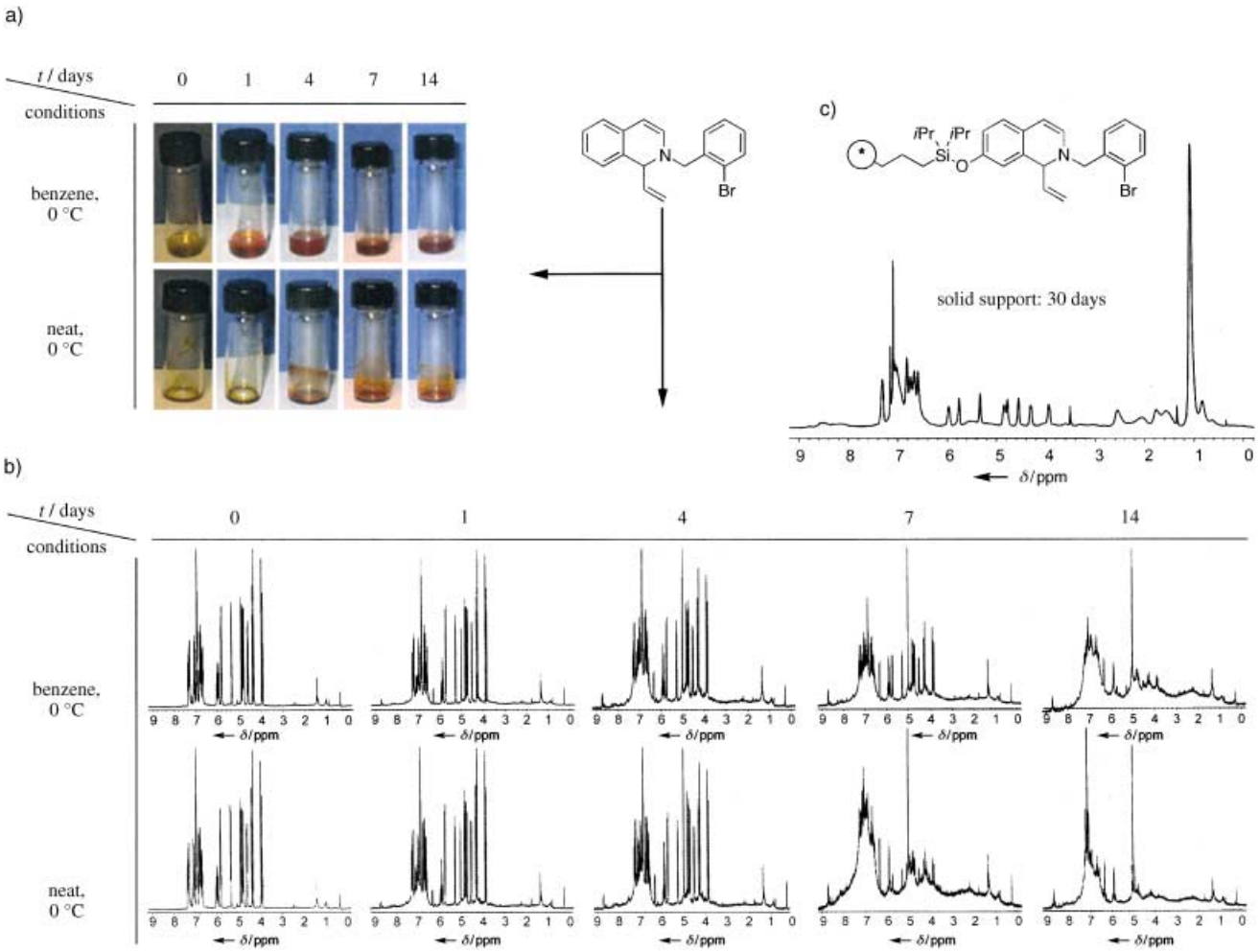


Figure 3. Comparison of the stability of enamine intermediates in solution versus attached to the solid support. a) Photographs of the dihydroisoquinoline analogous to **4**, stored neat at 0 °C or frozen in [D_6]benzene (50 mg/0.40 mL) at 0 °C; b) ^{1}H NMR of the same dihydroisoquinoline stored either neat at 0 °C or frozen in [D_6]benzene (50 mg/0.40 mL) at 0 °C; c) MAS ^{1}H NMR spectrum of the enamine **4** after 30 days at room temperature on the solid support.

the three atoms shared by all of the molecules (the nitrogen atom and two sp^2-hybridized carbon atoms of the heterocyclic core) gives a clear picture of the skeletal diversity provided by the three-step synthetic pathway (Figure 4). The overlaid skeletons suggest that the molecules synthesized by this pathway will display chemical information in three dimensions differentially, thereby increasing the number of potential small-molecule–biological-target interactions.

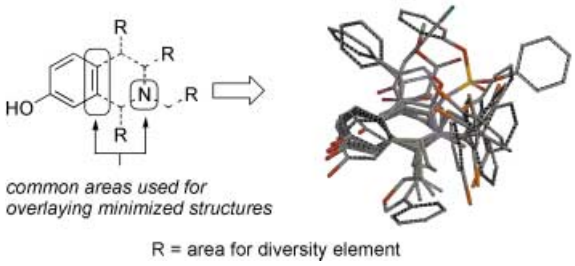


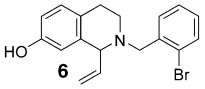
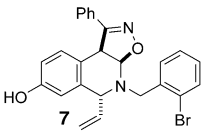
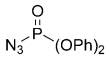
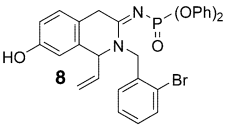
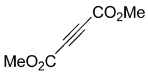
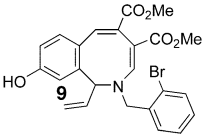
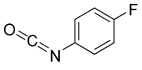
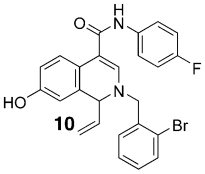
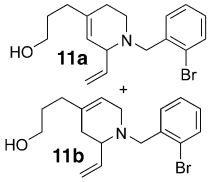
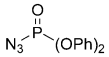
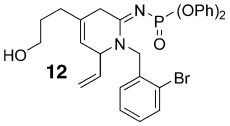
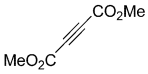
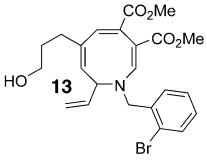
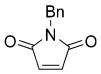
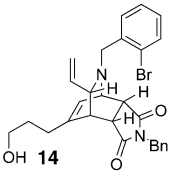
Figure 4. The AM1 minimized-energy conformations of the isoquinoline-based skeletons were calculated, and their structures were aligned with respect to the three common atoms. The overlay provides a visualization of the skeletal diversity of the products of the three-step synthetic pathway.

The synthetic strategy presented herein enables the synthesis of skeletally diverse alkaloid-like compounds in only three steps. Key to the synthesis is the generation and isolation of reactive dihydropyridines and dihydroisoquinolines, which are useful substrates for a variety of skeleton-determining transformations. This synthetic sequence leads to twelve distinct skeletons, all of which contain a hydroxy group, which is important for the microarray technology used in protein-binding assays,[19] and all with high purity (80 % purity on average by LC–MS). The modularity of the synthetic pathway allows for the efficient incorporation of building blocks at a number of key sites on the skeletons. Efforts are currently underway to develop a library of alkaloid-like compounds through this synthetic pathway.

Received: December 5, 2003 [Z53466]

Keywords: diversity-oriented synthesis · enamines · nitrogen heterocycles · reactive intermediates · solid-phase synthesis

Table 1: Skeletal-diversification reactions.

Entry	Enamine	Reagents	Product[a]	Yield [%][b]	Purity [%][c]
1[d]	**4**	$Na(CN)BH_3$ CF_3CH_2OH	 **6**	69	75
2[e]	**4**		 **7**	65	58
3[f]	**4**		 **8**	60	81
4[g]	**4**		 **9**	69	84
5[h]	**4**		 **10**	66	60
6[d]	**5**	$Na(CN)BH_3$ CF_3CH_2OH	 **11a** + **11b**	55	85
7[f]	**5**		 **12**	50	85
8[g]	**5**		 **13**	53	88
9[i]	**5**		 **14**	54	93

[a] Product following cleavage from the solid support. [b] Yield over two steps based upon weight of compound after cleavage from the solid support with HF·pyridine. [c] Purity determined by LC–MS (214 and 254 nm, and total ion current) as a percentage of the total peak area (see Supporting Information for details). [d] $Na(CN)BH_3$: 5 equivalents, room temperature, 16 h. [e] Oxime chloride: 5 equivalents, triethylamine (TEA): 10 equivalents, room temperature, 16 h. Longer reaction times lead to bis(cycloadduct) formation in 82% yield with 75% purity. [f] Azide: 10 equivalents, room temperature, 5 h. [g] DMDA: 10 equivalents, room temperature, 16 h. [h] Isocyanate: 20 equivalents, 90°C, 5 h. [i] Maleimide: 10 equivalents, toluene, 50°C, 16 h, isolated as a single diastereomer.

[1] S. L. Schreiber, *Chem. Eng. News* **2003**, *81*, 51 – 61.

[2] a) R. Breinbauer, I. R. Vetter, H. Waldmann, *Angew. Chem.* **2002**, *114*, 3002 – 3015; *Angew. Chem. Int. Ed.* **2002**, *41*, 2878 – 2890; b) S. L. Schreiber, *Science* **2000**, *287*, 1964 – 1969; c) M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48 – 60; *Angew. Chem. Int. Ed.* **2004**, *43*, 46 – 58.

[3] a) R. A. Stavenger, S. L. Schreiber, *Angew. Chem.* **2001**, *113*, 3525 – 3529; *Angew. Chem. Int. Ed.* **2001**, *40*, 3417 – 3421; b) O. Kwon, S. B. Park, S. L. Schreiber, *J. Am. Chem. Soc.* **2002**, *124*, 13402 – 13404.

[4] a) D. S. Tan, M. A. Foley, M. D. Shair, S. L. Schreiber, *J. Am. Chem. Soc.* **1998**, *120*, 8565 – 8566; b) S. M. Sternson, J. A. Louca, J. C. Wong, S. L. Schreiber, *J. Am. Chem. Soc.* **2001**, *123*, 1740 – 1747.

[5] a) G. C. Micalizio, S. L. Schreiber, *Angew. Chem.* **2002**, *114*, 160 – 162; *Angew. Chem. Int. Ed.* **2002**, *41*, 152 – 154; b) M. D. Burke, S. L. Schreiber, *Science* **2003**, *302*, 613 – 618.

[6] *The Chemistry of Enamines*, *Vol. 1 & 2* (Ed.: Z. Rappoport), Wiley, New York, **1994**.

[7] a) H. E. Blackwell, L. Perez, R. A. Stavenger, J. A. Tallarico, E. C. Eatough, M. A. Foley, S. L. Schreiber, *Chem. Biol.* **2001**, *8*, 1167 – 1182; b) P. A. Clemons, A. N. Koehler, B. K. Wagner, T. G. Sprigings, D. R. Spring, R. W. King, S. L. Schreiber, *Chem. Biol.* **2001**, *8*, 1183 – 1195.

[8] J. A. Tallarico, K. M. Depew, H. E. Pelish, N. J. Westwood, C. W. Lindsley, M. D. Shair, S. L. Schreiber, M. A. Foley, *J. Comb. Chem.* **2001**, *3*, 312 – 318.

[9] a) Additional building blocks can be used in these steps, including alkyl and aryl Grignard reagents, aryl zinc reagents, and non-benzylic alkyl bromides; details will be presented in a subsequent manuscript; b) initial attempts at palladium-catalyzed intramolecular cyclizations with compound **4** resulted in complete cleavage of the material from the solid support.

[10] a) L. M. Thiessen, J. A. Lepoivre, F. C. Alderweireldt, *Tetrahedron Lett.* **1974**, *15*, 59 – 62; b) T. Onaka, *Tetrahedron Lett.* **1971**, *12*, 4395 – 4398; c) R. F. Francis, J. T. Wisener, J. M. Paul, *J. Chem. Soc. D* **1971**, 1420; R. Grashey, R. Huisgen, *Chem. Ber.* **1959**, *92*, 2641; d) C. S. Giam, S. D. Abbott, *J. Am. Chem. Soc.* **1971**, *93*, 1294 – 1296.

[11] a) R. Lavilla, *J. Chem. Soc. Perkin Trans. 1*, **2002**, 1141 – 1156; b) D. M. Stout, A. I. Meyers, *Chem. Rev.* **1982**, *82*, 223 – 243; c) U. Eisner, J. Kuthan, *Chem. Rev.* **1972**, *72*, 1 – 42; d) F. W. Fowler in *Comprehensive Heterocyclic Chemistry*, *Vol. 2* (Ed.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, p. 365.

[12] Z. Kiparissides, R. H. Fichtner, J. Poplawski, B. C. Nalliah, D. B. MacLean, *Can. J. Chem.* **1980**, *58*, 2770 – 2779; trifluoroethanol was employed instead of acetic acid to avoid compound cleavage from the solid support.

[13] a) A. J. Bicknell, N. W. Hird, S. A. Readshaw, *Tetrahedron Lett.* **1998**, *39*, 5869 – 5872; b) O. Tsuge, S. Kanemasa, S. Takenaka, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3631 – 3635.
[14] a) S. Kitane, L. Chraibi, M. Soufiaoui, *Tetrahedron* **1992**, *48*, 8935 – 8946; b) S. Yamada, Y. Hamada, K. Ninomiya, T. Shioiri, *Tetrahedron Lett.* **1976**, 4749 – 4752.
[15] a) M. M. Bamatraf, J. M. Vernon, G. D. Wilson, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1647 – 1648; b) R. M. Acheson, G. Paglietti, P. A. Tasker, *J. Chem. Soc. Perkin Trans. 1*, **1974**, 2496 – 2500; c) P. G. Lehman, *Tetrahedron Lett.* **1972**, 4863 – 4864.
[16] Isocyanates have been reported to undergo thermal [2+2] cycloadditions with enamines to produce lactams as well as the conjugated amide: a) C. Nisole, P. Uriac, J. Huet, L. Toupet, *J. Chem. Res. Miniprint* **1991**, *8*, 1914 – 1952; b) R. F. Abdulla, K. H. Fuhr, *J. Med. Chem.* **1975**, *18*, 625 – 627; c) J. Goerdeler, M.-L. Tiedt, K. Nandi, *Chem. Ber.* **1981**, *114*, 2713 – 2722.
[17] For examples of Diels–Alder reactions that involve 1,2-dihydropyridines, see: a) M. A. Foley, PhD thesis, Harvard University, Cambridge, Massachusetts, **2001**; b) S. Druey, *Helv. Chim. Acta* **1959**, *42*, 1960 – 1970; c) H. A. Staab, H.-J. Hasselbach, *Tetrahedron Lett.* **1985**, *26*, 5979 – 5982.
[18] Computational calculations were performed with the Spartan software package: Spartan'02, Wavefunction, Inc., Irvine, CA. See Supporting Information for details.
[19] a) P. J. Hergenrother, K. M. Depew, S. L. Schreiber, *J. Am. Chem. Soc.* **2000**, *122*, 7849 – 7850; b) D. Barnes-Seeman, S. B. Park, A. N. Koehler, S. L. Schreiber, *Angew. Chem.* **2003**, *115*, 2478 – 2481; *Angew. Chem. Int. Ed.* **2003**, *42*, 2376 – 2379.

