ACS Combinatorial Science

Letter

pubs.acs.org/acscombsci

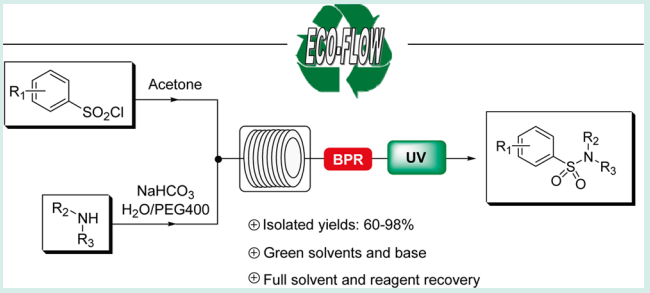
# Building a Sulfonamide Library by Eco-Friendly Flow Synthesis

Antimo Gioiello,* Emiliano Rosatelli, Michela Teofrasti, Paolo Filipponi, and Roberto Pellicciari

Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo, 1, 06123 Perugia, Italy.

Supporting Information

**ABSTRACT:** A rapid and eco-friendly synthesis of a sulfonamide library under flow conditions is described. The study illustrates an efficient, safe, and easily scalable preparation of sulfonamides by use of a meso-reactor apparatus, thus demonstrating the impact of flow technologies within drug discovery. Waste minimization, employment of green media, and nontoxic reactants are achieved by the optimization of the flow setup and experimental protocol designed to sequentially synthesize primary, secondary, and tertiary sulfonamides. Isolation of the products involves only extraction and precipitation affording pure compounds in good to high yields without further purification for biological evaluation.




**KEYWORDS:** *sulfonamide, flow chemistry, eco-friendly synthesis, compound library*

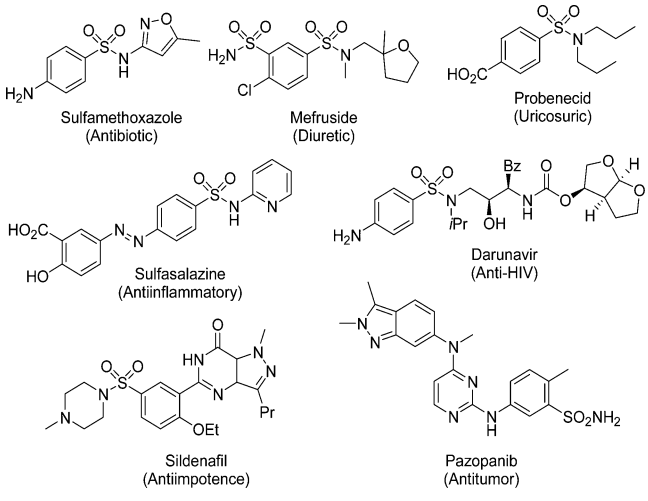
In recent years, medicinal chemistry has faced a significant evolution in both approaches and methodologies because of the advent of new and innovative technologies. In this context, flow chemistry has rapidly turned into one of the techniques that may revolutionize the synthetic sector of drug discovery from a quality and safety standpoint, as well as in terms of cost-effectiveness and environmental impact.[1−4] The main potential advantages of the flow approach include the following: high control of reaction parameters, possibility to conduct reactions at high temperature and pressure (process intensification), rapid and automated compound library preparation, telescoping reactions, in-line purification, easy reproducibility, and scale-up.

As part of our medicinal chemistry efforts, we needed to develop a facile and rapid synthesis of sulfonamides that was suitable for preparing a wide variety of compounds. To accomplish this task, we sought to explore the possibility to employ flow synthesis and eco-friendly protocols, which could be also useful for large scale preparations.

Sulfonamides represent a very important class of compounds in medicinal and synthetic chemistry.[5−7] Indeed, sulfonamide functionality constitutes the structural motif of a variety of drugs (Chart 1) and bioactive compounds endowed with antibacterial, antitumor, anti-inflammatory, hypoglycemic, and protease inhibitory activity among others.[6,7] Therefore, the search for a new and efficient preparation of sulfonamides is still of great interest.

Among the many strategies reported for the synthesis of sulfonamide derivatives,[8−13] the classical approach from amino compounds and sulfonyl chlorides has attracted considerable attention thanks to the good reactivity and simplicity of the experimental protocols.[14−19] The main drawbacks of this methodology include the use of organic amine bases to scavenge the acid (HCl) that is generated during the reaction, high temperatures needed for the less reactive substrates, as well as laborious purifications often required when competing side reactions occur.[20] Recently, a sulfonamide synthesis has been described in aqueous media and under dynamic control.[21] The method avoided the use of organic bases and chromatographic purifications and was applied to a variety of arylsulfonyl chlorides and amines. Noteworthy, the reactions were carried out after the pH adjustment of the solution, they took several hours for completion and can be employed mainly to primary aryl amino derivatives partially soluble in water. A fully

**Chart 1. Examples of Sulfonamide-Containing Therapeutic Drugs**



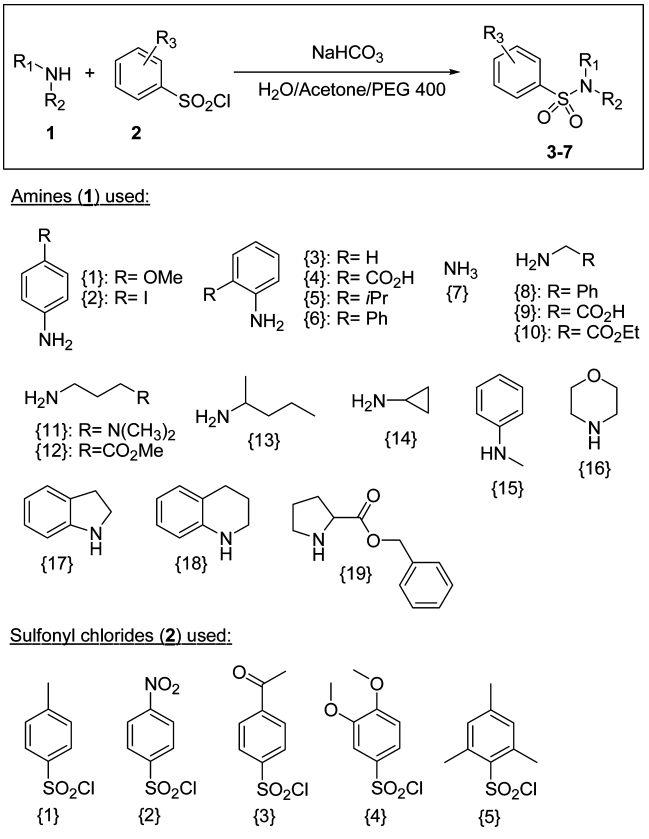

**Received:** January 23, 2013
**Revised:** March 18, 2013
**Published:** March 20, 2013

automated two-step flow process was reported for the preparation of a 48-member library of secondary sulfonamides.[22] It included the N-monoalkylation of primary sulfonamides through a resin catch and release strategy followed by removal of the Boc-protecting group. More recently, a combination of flow and batch chemistries was applied for the synthesis of trisubstituted pyrrolidines.[23] In this case, the sulfonylation reaction was conducted in batch modality by treatment of the pyrrolidine intermediates with a set of sulfonyl chlorides in the presence of Hunig's base in DMF.

In continuation of our recent interest in the development of novel flow methodologies for the synthesis of medicinally relevant compounds,[24] we demonstrate how to perform a green, scalable, one-pot flow preparation of primary, secondary, and tertiary sulfonamides capable of delivering pure products without the use of tedious work-ups and purifications. Starting with classical laboratory batch-screen, we decided to study the reaction between *p*-anisidine (**1**){*1*} and tosyl chloride (**2**){*1*} under Schotten–Baumann conditions (Scheme 1) as a model system for the fine-tuning of the experimental parameters and the implementation of the flow setup.

**Scheme 1. Reaction of Amines with Sulfonyl Chlorides in Flow Conditions**




The initial attempts were not very encouraging. As expected, the reaction conducted in acetone–aqueous, basic ($Na_2CO_3$ or NaOH) solution gave poor yields because of hydrolysis of the *p*-toluensulfonyl chloride (data not shown). In this respect, it has been reported that the optimal pH for minimizing the occurrence of hydrolysis is between 8 and 9.[21] We thus considered the use of $NaHCO_3$ as the base being endowed with a p$K_a$ and pH value of 10.3 and 8.4, respectively. However, the use of water and acetone as the solvent system at different ratios did not fit for a flow process due to the formation of precipitates. The addition of phase transfer agents, such as $Bu_4NBr$,[21] can give satisfactory results only when the reactions were performed with liquid reagents. The problem was resolved by using polyethylene glycol 400 (PEG 400) as an additional organic cosolvent for the reaction. PEGs have been widely used as powerful and eco-friendly reaction medium for several synthetic transformations.[25−29] In particular, PEG 400 is relatively cheap, readily recyclable, biodegradable and water-soluble making it easily removable by simple workup operations. Moreover, PEG 400 is endowed with a viscosity value of 90 cP thus ensuring the flow system to operate properly. The best result in terms of solubility was obtained with a solution of $H_2O$/acetone/PEG 400 1:2:1 (v/v/v).

Having established the optimal solvent system, the reactions were then carried out in a flow meso-reactor equipped with a two-loop injection system, two pumps devoted to the acetone and $H_2O$ reservoir of solvent, a 10 mL reactor, a back pressure regulator (BPR), a UV detector and a fraction collector (Figure 1). With the aim to find the experimental conditions that would

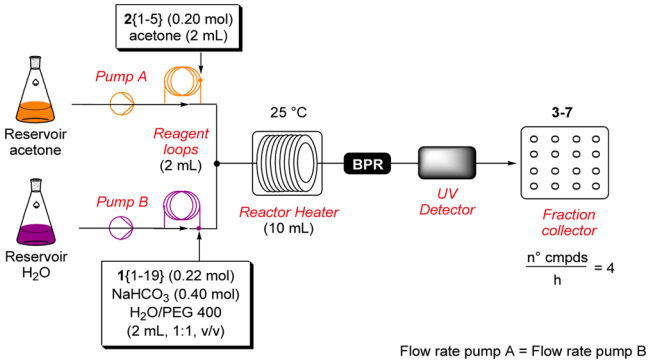



**Figure 1.** Flow setup used during the optimization of the reaction conditions. BPR = back pressure regulator; cmpds = compounds; h = hour.

guarantee the highest productivity and rapidity, a series of experiments were performed varying the residence time (flow rate) (Table 1). Temperature was fixed at 25 °C, and the reactions were performed by loop injection of two stock solutions: the first one was constituted with *p*-anisidine (**1a**) (0.22 mol) and $NaHCO_3$ (0.40 mol) dissolved in water/PEG 400 (2 mL, 1:1, v/v), and the second one with an acetone solution (2 mL) of tosyl chloride (**2a**) (0.20 mol). Two equivalents of $NaHCO_3$ were sufficient to ensure HCl trapping

**Table 1. Flow Rate Effect**[a]

| entry | flow rate (mL min$^{-1}$)[b] | yield (%)[c] |
|---|---|---|
| 1 | 0.2 | 91 |
| 2 | 0.3 | 100 |
| 3 | 0.4 | 100 |
| 4 | 0.5 | 100 |
| 5 | 0.75 | 98 |
| 6 | 1 | 94 |
| 7 | 1.5 | 76 |
| 8 | 2.0 | 74 |

[a]**1**{1}/**2**{1}/$NaHCO_3$ = 1/0.9/2; *T* = 25 °C; BPR = 100 psi. [b]Combined flow rate (pump A + pump B). [c]Determined by $^1$H NMR analysis of the crude reaction mixture.


dx.doi.org/10.1021/co400012m | *ACS Comb. Sci.* 2013, 15, 235−239

**Table 2. Overview of Synthesized Library Compounds and Purity Data**[a]

| entry | amine **1**{*1*−*19*} | sulfonyl chloride **2**{*1*−*5*} | sulfonamide (%)[b] | isolated yield (%)[c] |
|---|---|---|---|---|
| 1 | {*1*} | {*1*} | **3** (98) | 92 |
| 2 | {*2*} | {*1*} | **3** (90) | 62 |
| 3 | {*3*} | {*1*} | **3** (100) | 97 |
| 4 | {*4*} | {*1*} | **3** (86) | 70 |
| 5 | {*6*} | {*1*} | **3** (98) | 89 |
| 6 | {*7*} | {*1*} | **3** (100) | 98 |
| 7 | {*8*} | {*1*} | **3** (100) | 94 |
| 8 | {*9*} | {*1*} | **3** (98) | 86 |
| 9 | {*11*} | {*1*} | **3** (92) | 77 |
| 10 | {*13*} | {*1*} | **3** (100) | 97 |
| 11 | {*14*} | {*1*} | **3** (98) | 87 |
| 12 | {*15*} | {*1*} | **3** (95) | 85 |
| 13 | {*16*} | {*1*} | **3** (100) | 93 |
| 14 | {*17*} | {*1*} | **3** (96) | 90 |
| 15 | {*18*} | {*1*} | **3** (100) | 95 |
| 16 | {*3*} | {*2*} | **4** (98) | 88 |
| 17 | {*4*} | {*2*} | **4** (89) | 60 |
| 18 | {*5*} | {*2*} | **4** (93) | 84 |
| 19 | {*8*} | {*2*} | **4** (100) | 97 |
| 20 | {*10*} | {*2*} | **4** (97) | 90 |
| 21 | {*14*} | {*2*} | **4** (93) | 82 |
| 22 | {*1*} | {*3*} | **5** (100) | 96 |
| 23 | {*2*} | {*3*} | **5** (91) | 68 |
| 24 | {*3*} | {*3*} | **5** (98) | 82 |
| 25 | {*8*} | {*3*} | **5** (100) | 98 |
| 26 | {*10*} | {*3*} | **5** (93) | 78 |
| 27 | {*3*} | {*4*} | **6** (100) | 96 |
| 28 | {*4*} | {*4*} | **6** (85) | 58 |
| 29 | {*5*} | {*4*} | **6** (100) | 96 |
| 30 | {*8*} | {*4*} | **6** (100) | 97 |
| 31 | {*12*} | {*4*} | **6** (90) | 80 |
| 32 | {*13*} | {*5*} | **7** (85) | 76 |
| 33 | {*16*} | {*5*} | **7** (95) | 82 |
| 34 | {*3*} | {*5*} | **7** (100) | 83 |
| 35 | {*1*} | {*5*} | **7** (100) | 87 |
| 36 | {*2*} | {*5*} | **7** (98) | 72 |
| 37 | {*17*} | {*5*} | **7** (88) | 81 |
| 38 | {*18*} | {*5*} | **7** (86) | 71 |
| 39 | {*19*} | {*5*} | **7** (90) | 76 |

[a] **1**/**2**/$NaHCO_3$ = 1/0.9/2; $T$ = 25 °C; BPR = 100 psi; combined flow rate = 0.5 mL $min^{-1}$. [b] Determined by $^1H$ NMR analysis of the crude reaction mixture. [c] Determined after extraction.

and the correct value of pH at the end of the reaction (pH 8). After the injection into the flow stream and the switching of the valves through the loops, the two solutions were mixed in a T-junction, pumped through the coil reactor, and the output collected using a UV detector and a fraction collector (Figure 1). The conversion of the substrate and the relative reaction yields were determined by NMR analysis of the crude mixtures.

As illustrated in Table 1, a high efficiency was maintained with a flow rate ranging from 0.2 to 1.0 mL $min^{-1}$, obtaining a quantitative conversion with a total flow rate of 0.5 mL $min^{-1}$. The collected product was quenched with 3 N HCl and extracted with $Et_2O$ to give the desired sulfonamide **3** with high purity (>95%) without further purifications.

Using the optimized experimental conditions, the reaction was applied to a variety of amines and sulfonyl chlorides (Scheme 1) according to the flow setup depicted in Figure 1. The scope was not to obtain a full combinatorial library with all possible combinations but, rather, to prepare a diverse set of products spanning different structural and physicochemical properties. Thus, reagent solutions were injected in sequence via loops and pumped at equal flow rates (0.25 mL $min^{-1}$) to meet at a T-piece mixer. After it passed the reactor heater, the flow stream went through the UV detector useful to indicate the volume of reaction mixture to be collected. In this way a large number of compounds were prepared in a single run consisting of amine variations.

The analysis of the results showed that sulfonamides were formed in good to high yields (Table 2) and clearly demonstrated the efficiency of the method to prepare arrays of sulfonamides in a sequential flow-through process. In particular, the reactions of primary aryl amines having both electron-donating and electron-withdrawing groups proceeded with excellent and good yields, respectively (Table 2). These results were particularly interesting because under classical batch conditions, electron-withdrawing substituted amines **1**{*1*−*2,4*} gave moderate and low yields and required several


dx.doi.org/10.1021/co400012m | ACS Comb. Sci. 2013, 15, 235−239

hours to reach completation. Notably, less reactive secondary **1**{*15*−*19*} and alkyl amines **1**{*11*−*14*} and various arylsulfonyl chlorides **2**{*1*−*5*} also worked well in the reaction. All the products **3**−**7** were isolated by simple extraction and then analyzed by GC-MS and NMR spectroscopy. In all cases, the desired compounds were obtained in excess of 95% purity without further purification. No cross-contamination was detected in any instance.

**Scale Up.** One of the main advantages of flow synthesis is the easy scaling-up either by continuous running or by the numbering up of flow reactors. As an example, we have applied our method for the large preparation of probenecid (**10**), a prototypical uricosuric drug also used to treat patients with renal impairment as an adjunct to antibacterial therapy. The in-flask patented synthesis of this compound has been reported to proceed in one or two steps with an overall yield ranging from 41% to 65%.[30−32] Thus, 4.4 g of 4-(chlorosulfonyl)benzoic acid (**8**) were dissolved in 200 mL of acetone and processed with 5.6 mL of dipropylamine (**9**) and 3.4 g of $NaHCO_3$ in 200 mL of a water/PEG 400 solution (Figure 2). The crude flow stream

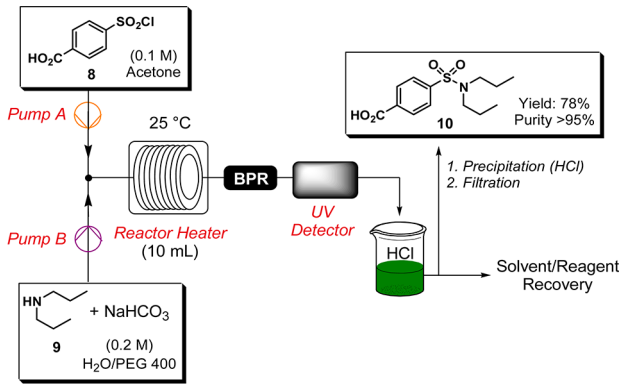



**Figure 2.** Flow scale up of probenecib.

was dropped into an aqueous solution of HCl 3 N (pH< 2) providing **9** in 78% yield and with a purity greater than 95% by simple precipitation. The filtered solution was then washed with diethyl ether, distilled to recycle acetone, and water used for the reaction, and treated with a solution of NaOH and Amberlist A15 for the recovery of PEG 400 and of the excess of amine. Additionally, the ether used in the workup was also recovered and used in following reactions.

In conclusion, we have developed the synthesis of sulfonamides by employing flow-based technology to aid the preparation of a wide variety of compounds and to facilitate the scale-up operations. This work could therefore support medicinal chemistry programs at various stages as the hit-to-lead, lead-optimization and lead candidate scale-up.

Several aspects of this continuous flow process are noteworthy. First, so far this is the only example of an eco-benign synthesis of sulfonamide library in a single continuous step. Reactions were performed at room temperature using an acetone solution of sulfonyl chlorides along with an aqueous solution of the amines and $NaHCO_3$, a reagent flow rate of 0.5 mL $min^{-1}$ and a residence time of approximately 15 min. PEG 400 was essential to achieve the complete solubilization of organic and inorganic reactants. As previously noted, the isolation of the desired products was achieved without the use of column purifications, in high yield and affording quality material ready for biological screenings. Importantly, the method can be easily automated through the use of an appropriate software and autosampler. Second, since this method works efficiently with both primary and secondary amines and various sulfonyl chlorides, it provides a convenient route for a wide variety of sulfonamides. Finally, we have demonstrated the utility of this method for large scale preparation of probenecid (**9**) obtained in a single step in 78% yield and purified by precipitation with a purity of 95%. Moreover, the solvents used can be easily recovered and reused for further reactions reducing waste, pollution and costs (E-factor = 0.66).[33]

## ■ ASSOCIATED CONTENT

### Supporting Information

Description of the experimental procedures, analytical protocols, NMR spectra, and MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*Address: Laboratory of Medicinal and Advanced Synthetic Chemistry (Lab MASC), Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo, 1, 06123 Perugia, Italy. E-mail: antimo@chimfarm.unipg.it. Fax: +39.075.5855160. Tel: +39.075.5852318.

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

## ■ ABBREVIATIONS

PEG, polyethylene glycol; BPR, back pressure regulator

## ■ REFERENCES

(1) Sanz, L. M.; Susanne, F. Continuous Flow Synthesis. A Pharma Perspective. *J. Med. Chem.* **2012**, *55*, 4062−4098.
(2) Baumann, M.; Baxendale, I. R.; Ley, S. V. The Flow Synthesis of Heterocycles for Natural Product and Medicinal Chemistry Applications. *Mol. Diversity* **2011**, *15*, 613−630.
(3) Wiles, C.; Watts, P. Continuous Flow Reactors: A Perspective. *Green Chem.* **2012**, *14*, 38−54.
(4) Wegner, J.; Ceylan, S.; Kirschning, A. Ten Key Issues in Modern Flow Chemistry. *Chem. Commun.* **2011**, *47*, 4583−4592.
(5) Wilden, J. D. The Sulphonamide Motif as a Synthetic Tool. *J. Chem. Res.* **2010**, 541−548.
(6) Supuran, C .T.; Casini, A.; Scozzafava, A. Protease Inhibitors of the Sulfonamide Type: Anticancer, Antiinflammatory, and Antiviral Agents. *Med. Res. Rev.* **2003**, *5*, 535−558.
(7) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. Anticancer and Antiviral Sulfonamides. *Curr. Med. Chem.* **2003**, *10*, 925−953.
(8) Wright, S. W.; Hallstrom, K. N. A Convenient Preparation of Heteroaryl Sulfonamides and Sulfonyl Fluorides from Heteroaryl Thiols. *J. Org. Chem.* **2006**, *71*, 1080−1084.
(9) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Vakulenko, A. V.; Tao, H. *N*-Sulfonylbenzotriazoles as Advantageous Reagents for C-Sulfonylation. *J. Org. Chem.* **2005**, *70*, 9191−9197.
(10) Caddick, S.; Wilden, J. D.; Judd, D. B. Direct Synthesis of Sulfonamides and Activated Sulfonate Esters from Sulfonic Acids. *J. Am. Chem. Soc.* **2004**, *126*, 1024−1025.

(11) Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. M. Facile One-Pot Synthesis of Aromatic and Heteroaromatic Sulfonamides. *J. Org. Chem.* **2003**, *68*, 8274−2876.
(12) Lee, J. V.; Louie, Y. Q.; Walsh, D. P.; Chang, Y.-T. Nitrophenol Resins for Facile Amide and Sulfonamide Library Synthesis. *J. Comb. Chem.* **2003**, *5*, 330−335.
(13) Frost, C. G.; Hartley, J. P.; Griffin, D. Catalytic Arylation of Sulfamoyl Chlorides: A Practical Synthesis of Sulfonamides. *Synlett* **2002**, *11*, 1928−1930.
(14) Holmes, T. J. J.; Lawton, R. G. Preparation of Nonsymmetrical *p*-Benzoquinone Diimides for Evaluation as Protein Cleavage Reagents. *J. Org. Chem.* **1983**, *48*, 3146−3150.
(15) Sonntag, N. O. V. The Reactions of Aliphatic Acid Chlorides. *Chem. Rev.* **1953**, *52*, 237−476.
(16) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. Novel 1,4-Benzodiazepines from Acylnitroso-Derived Hetero-Diels−Alder Cycloadducts. *Org. Lett.* **2002**, *4*, 139−141.
(17) Hu, W.; Guo, Z.; Chu, F.; Bai, A.; Yi, X.; Cheng, G.; Li, J. Synthesis and Biological Evaluation of Substituted 2-Sulfonyl-Phenyl-3-Phenyl-Indoles: A New Series of Selective COX-2 Inhibitors. *Bioorg. Med. Chem.* **2003**, *11*, 1153−1160.
(18) Medebielle, M.; Onomura, O.; Keirouz, R.; Okada, E.; Yano, H.; Terauchi, T. Indium-Mediated Reformatsky-Type Reaction of *β*-Aminovinyl Chlorodifluoromethyl Ketones with Heteroaryl Aldehydes. *Synthesis* **2002**, *17*, 2601−2608.
(19) Wydysh, E. A.; Medghalchi, S. M.; Vadlamudi, A.; Townsend, C. A. Design and Synthesis of Small Molecule Glycerol 3-Phosphate Acyltransferase Inhibitors. *J. Med. Chem.* **2009**, *52*, 3317−3327.
(20) Yasuhara, A.; Kameda, M.; Sakamoto, T. Selective Monodesulfonylation of *N*,*N*-Disulfonylarylamines with Tetrabutylammonium Fluoride. *Chem. Pharm. Bull.* **1999**, *47*, 809−812.
(21) Deng, X.; Mani, N. S. A Facile, Environmentally Benign Sulfonamide Synthesis in Water. *Green Chem.* **2006**, *8*, 835−838.
(22) Griffiths-Jones, C. M.; Hopkin, M. D.; Jönsson, D.; Ley, S. V.; Tapolczay, D. J.; Vickerstaffe, E.; Ladlow, M. Fully Automated Flow-Through Synthesis of Secondary Sulfonamides in a Binary Reactor System. *J. Comb. Chem.* **2007**, *9*, 422−430.
(23) Baumann, M.; Baxendale, I. R.; Kuratli, C.; Ley, S. V.; Martin, R. E.; Schneider, J. Synthesis of a Drug-Like Focused Library of Trisubstituted Pyrrolidines Using Integrated Flow Chemistry and Batch Methods. *ACS Comb. Science* **2011**, *13*, 405−413.
(24) Venturoni, F.; Gioiello, A.; Sardella, R.; Natalini, B.; Pellicciari, R. Continuous Flow Synthesis and Scale-up of Glycine- and Taurine-Conjugated Bile Salts. *Org. Biomol. Chem.* **2012**, *10*, 4109−15.
(25) Suman, L. J.; Sweety, S.; Bir, S. PEG-Assisted Solvent and Catalyst Free Synthesis of 3,4-Dihydropyrimidinones Under Mild Reaction Conditions. *Green Chem.* **2007**, *9*, 740−741.
(26) Ballini, R.; Barboni, L.; Palmieri, A. Improved Chemoselective, Ecofriendly Conditions for the Conversion of Primary Alkyl Halides into Nitroalkanes Under PEG 400. *Green Chem.* **2008**, *10*, 1004−1006.
(27) Kumar, R.; Chaudhary, P.; Nimesh, S.; Chandra, R. Polyethylene Glycol as a Non-Ionic Liquid Solvent for Michael Addition Reaction of Amines to Conjugated Alkenes. *Green Chem.* **2006**, *8*, 356−358.
(28) Vasudevan, V. N.; Rajender, S. V. Microwave-Accelerated Suzuki Cross-Coupling Reaction in Polyethylene Glycol (PEG). *Green Chem.* **2001**, *3*, 146−148.
(29) Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S.; Reddy, N. R. K. Poly(ethylene glycol) (PEG) as a Reusable Solvent Medium for Organic Synthesis. Application in the Heck Reaction. *Org. Lett.* **2002**, *4*, 4399−4401.
(30) Miller, C. U.S. Patent US2608507A, 1952.
(31) Gonzalez, J. M. Patent ES209068A1, 1953.
(32) Michman, M.; Weiss, M. Patent IL89366A, 1989.
(33) The estimation of E-factor value was determined by the ratio between total grams of waste generated per gram of pure probenecib.