



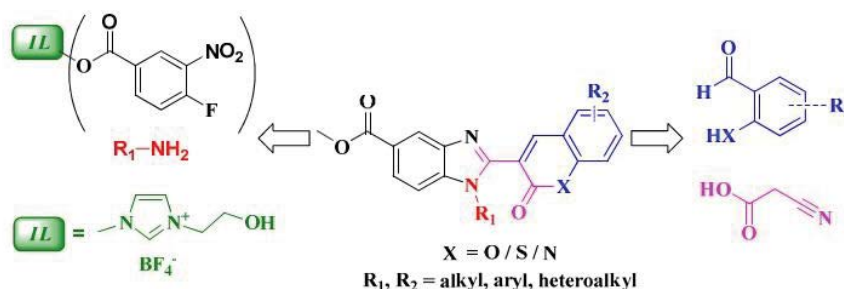
Rapid Access Synthesis of Quinoline, Chromene, Thiochromene Benzimidazol-Ylideneamines and Benzimidazolones via Traceless Tandem Transformation Under Microwave Irradiation on Ionic Liquid Support

Suman Thummanagoti, Chih Hau Chen and Chung Ming Sun*

Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan

Abstract

A fast and efficient protocol have explored to access the various benzimidazole constituted quinoline, chromene, thiochromenyldenamines and ones under microwave irradiation on ionic liquid support. Ionic liquid supported 4-floro3-nitrobenzoic acid has been used as a structural building block to generate these structural frameworks. After subsequent transformation the benzimidazole constituted cyanoacetic acid has been used as a molecular scaffold to generate various structural motifs. By taking the benzimidazole constituted cyanoacetic acid treated with various 2-substituted hydroxyl, amino and thiobanzaldehydes in order to get the described decorated structural scaffolds in the presence of organic base such as triethylamine. Under the same reaction conditions by leave the product and the cleavage of product from the support occurred sequence of transformations in traceless tandem manner. The same reaction under the hydrous conditions the imine hydrolysis leads to formation of quinoline, chromene, thiochromene benzimidazolones was described. The final compounds have been obtained high yield and purity making this procedure facile, practical, and rapid to execute.



Keywords: Benzimidazole; Chromene; Quinolone; Thiochromene; Microwave assisted synthesis; Ionic liquid support; Traceless synthesis; Synergistic approach; Rapid tandem transformations

Introduction

Benzimidazole fused or benzimidazoles constituted molecules have been a major source of new drugs to explore, and many successful drugs were originally synthesized to mimic the action of benzimidazole molecules found in nature [1-9]. The numerous benzimidazole embracing coumarin derivatives structural scaffolds containing compounds are highly diverse and often provide highly specific biological activities [10-12]. To this end the proposition that essentially all benzimidazole structural frameworks have some receptor binding capacity [13]. The benzimidazoles in combination with various quinazolines [14], chromen [15], and thiochromen [16-20] structures have attracted considerable attention. These heterocyclic ring-systems due to their presence in many naturally and synthetically derived molecules, which possess a wide range of biological properties and frequently, hold promising pharmaceutical potential [21]. 4-amino-3-benzimidazol-2-ylhydro quinolin-2-ones are a class of potent RTK inhibitors involved in important signal transduction pathways within the cell with attractive physicochemical and pharmacokinetic properties and significant efficacy in murine and human xenograft tumor models [22]. Compounds possessing coumarin, imidazole, benzothienopyrimidine or thiophene, benzopyran moieties represented basic structures screened for inhibitory activity against EGF, PDGF receptor tyrosine kinases and their inhibitory effects on tyrosine kinase pp60^{c-src} and p56^{lck} were evaluated [23-26]. Molecular scaffolds based on 3-benzimidazol-2-ylhydroquinolin-2-one analogues as inhibitors

of VEGF, PDGF, and fibroblast growth factor (FGF) receptor tyrosine kinases [27]. These compounds were also found to possess attractive pharmacokinetic characteristics and efficacy in several human tumor xenograft models [28,29]. The biological activities having the structural template coumarin derivatives shown as anticoagulant and antithrombotic activity of certain natural and Synthetic coumarin derivatives are known [30]. Certain coumarin derivatives are also reported as triplet sensitizers, anti-HIV agents; Lipid lowering agents antioxidants, inhibitors of lipid peroxidation and vasorelaxant agents, anti-inflammatory agents and free radical Scavengers [31-37]. In addition, two naturally occurring coumarins have been found to exhibit cytotoxicity across a selection of mammalian cancer cell lines [38]. Certain coumarin-3-carboxamides have been reported as inhibitors of protease, including A-chymotrypsin and human leukocyte elastase [39-44].

*Corresponding author: Chung Ming Sun, Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan, Tel: 03-5131511; E-mail: cmsun@mail.nctu.edu.tw

Received August 20, 2018; Accepted August 24, 2018; Published August 31, 2018

Citation: Thummanagoti S, Chen CH, Sun CM (2018) Rapid Access Synthesis of Quinoline, Chromene, Thiochromene Benzimidazol-Ylideneamines and Benzimidazolones via Traceless Tandem Transformation Under Microwave Irradiation on Ionic Liquid Support. Med Chem 8: 234-241. doi: 10.4172/2161-0444.1000518

Copyright: © 2018 Thummanagoti S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

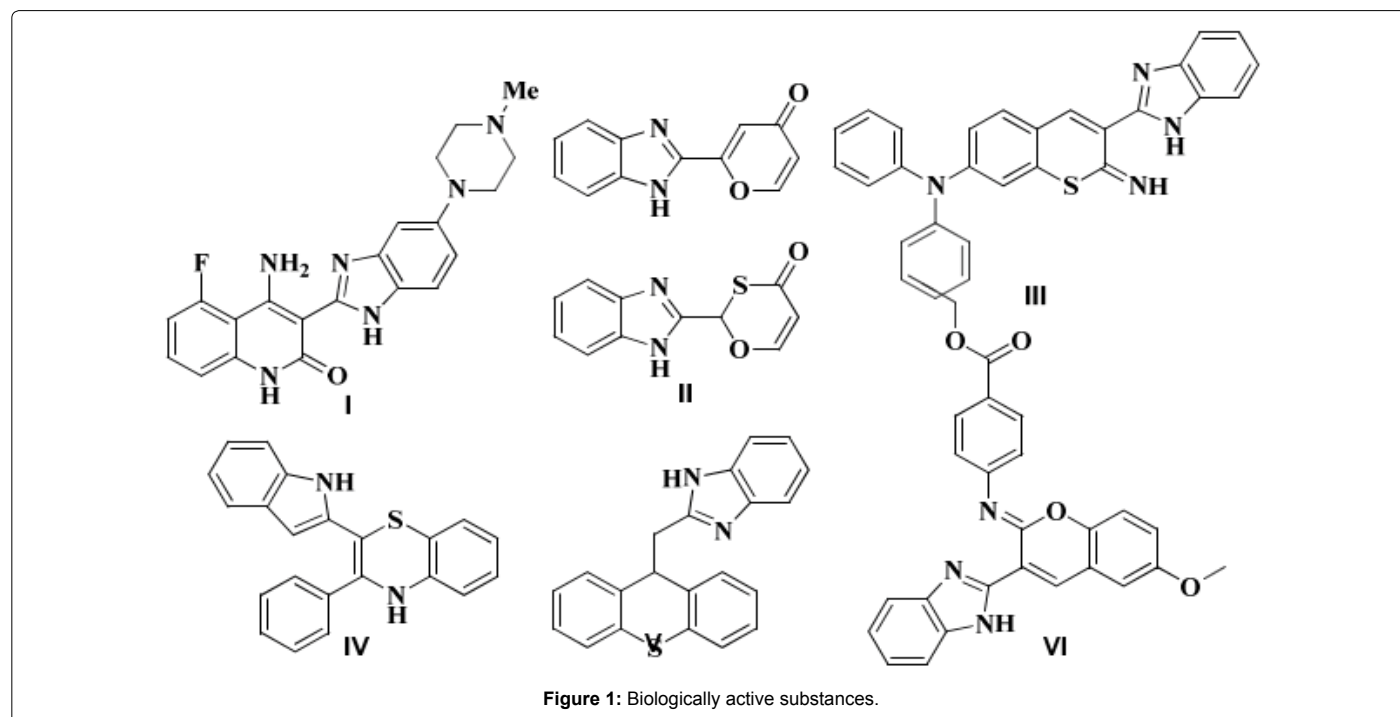
The current acceleration of expensive and time-consuming process drug discovery is a result of the combinatorial chemistry to generate large libraries of high structural diversity molecules, which are subsequently used in the high-throughput screening (HTS) process [45,46]. The use of solid phase and soluble polymer supported synthesis of combinatorial libraries; dramatically extended the structural diversity of the compounds tested in the drug discovery process and demonstrated that this approach is able to identify biologically active molecules far more rapidly than with the conventional solution phase synthetic approaches [47-49]. However the very effective, solid-supported synthesis suffers from a certain number of problems linked to the heterogeneous nature of the reaction conditions. In fact, the non-linear kinetic behavior, the unequal distributions, the sites which are non-accessible to reagents [50-52]. This limits the flexibility of the process to generate large compound libraries in shorter periods via different reactions [53]. The drawbacks of solid supports have led to the exploration of alternatives in order to find homogeneous reaction conditions [54,55]. In fact, the use of soluble polymers bypasses the difficulties of synthesis on solid supports whilst retaining a large number of its positive features [56]. This synthetic methodology has received considerable attention in various synthetic aspects [57,58]. However, the use of soluble polymer supports suffer from the drawback of low loading capacity, difficulties in the selective precipitation of the oligosaccharide-attached polymer, limited solubility during the synthesis of longer peptides, low aqueous solubility, the lack of solubility in ether solvents and energy intensive cooling required for purification [59,60]. In order to meet multi-faced drug discovery endeavor and overcome the debilitating, limiting factor for molecule submission to an assay, led researchers to develop ionic liquid supported synthetic methodologies by which large numbers of molecules possessing diverse chemical structures can be rapidly and efficiently synthesized [61-68]. The ionic liquid supported synthesis stands to benefit greatly from proper utilization of microwave energy due to their efficient microwave absorbance [69,70]. The synergetic synthetic chemistry has emerged as one of the most promising approaches to chemical library synthesis for the purpose of drug discovery [71,72].

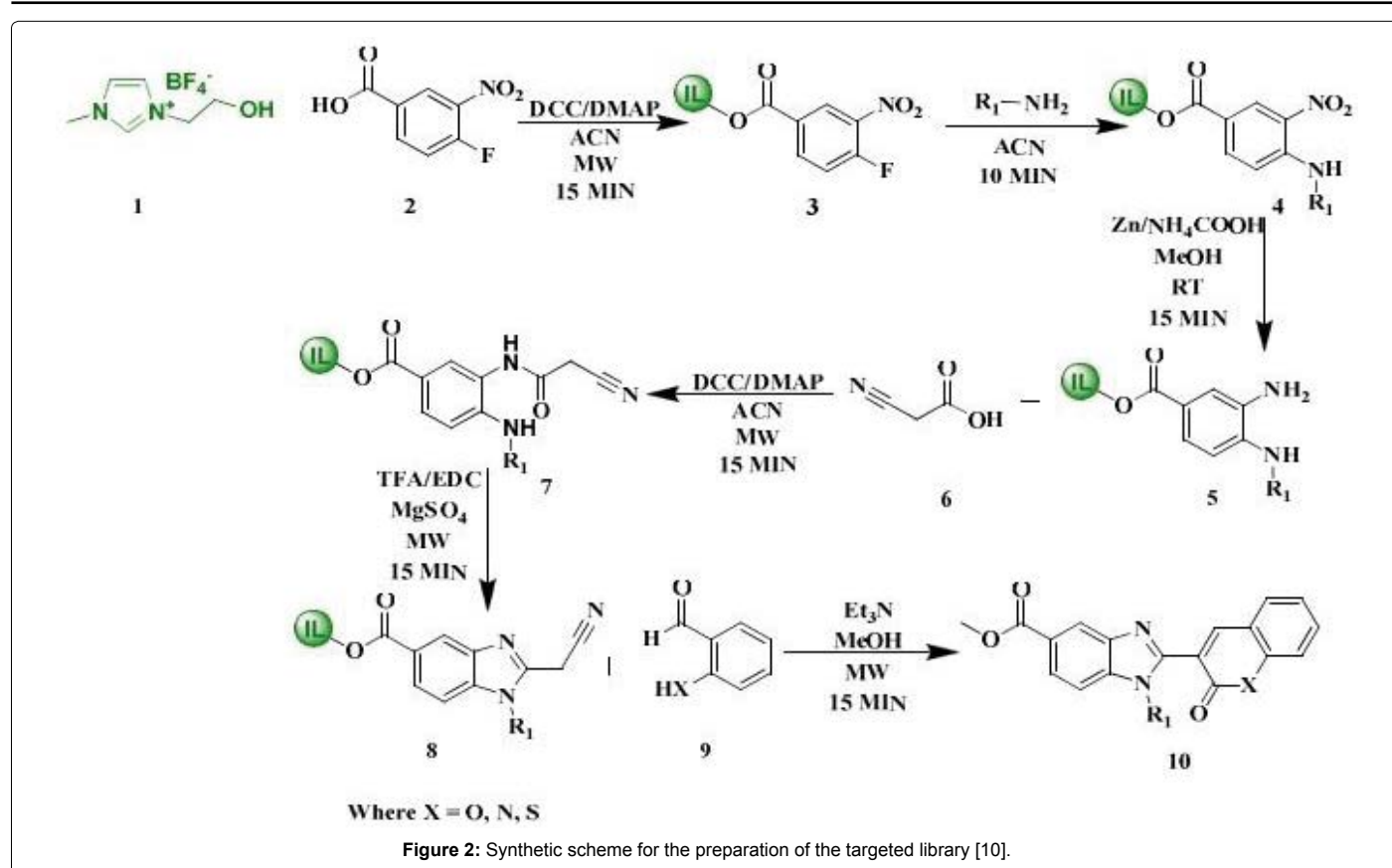
With the aim of develop more efficient synthetic methodologies and in continuation of our interest in developing combinatorial approaches to the synthesis of highly functionalized rapid access synthesis of quinoline, chromene, thiochromene benzimidazol-ylideneamines and benzimidazolones via traceless tandem transformation under microwave irradiation on Ionic Liquid support. Herein we describe a practical and rapid microwave-assisted method for the synthesis of highly functionalized quinoline, chromene, thiochromene benzimidazol-ylideneamines and benzimidazolones have been synthesized (Figures 1 and 2).

Experimental Section

General remarks

Melting points were determined on a Kofler melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) was accomplished on 0.2-mm pre-coated plates of silica gel 60 F-254 (Merck) or Neutral alumina oxide gel 60 F 254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. For preparative column chromatography, silica gel 60F 254 Merck (230-240 Mesh ASTM) and neutral alumina oxide gel 90 (Merck) were used. IR spectra were recorded on a BIORAD FTS 175°C spectrometer. ¹H NMR spectra were recorded on BRUKER AC 300 P (300 MHz), ¹³C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: δ value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants J is given in Hertz. The mass spectra (HRMS) were taken respectively on a MS/MS ZABSpec TOF Micromass (EBE TOF geometry) at an ionizing potential of 8 eV for the ILPs and on a VARIAN MAT 311 at an ionizing potential of 70 eV for the other compounds in the centre Regional de Mesures Physiques de l'Ouest (CRMPO, Rennes). Reactions under microwave irradiations were realized in the synthewave 402 apparatus (Merck EuroLab, Div. Prolabo, France) in quartz open reactor vessel fitted with a condenser or in the Discover apparatus (CEM, France). The





microwave instrument consists of a continuous focused microwave power output from 0 to 300W. All the experiments were performed using stirring option. The target temperature was reached with a ramp of 3 minutes and the chosen microwave power stay constant to hold the mixture at this temperature. The reaction temperature is monitored using calibrated infrared sensor and the reaction time includes the ramp period. Acetonitrile was distilled over calcium chloride after standing overnight and stored over molecular sieves (3Å). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Acros, Aldrich Chimie, Fluka France and used without further purification. The starting [HOC₂mim]⁺[X]⁻ ionic liquid phases 1a and 1b were synthesized according to our previous method for 1-(2-hydroxy-ethyl)-3-methyl-imidazolium hexafluorophosphate [HOC₂mim]⁺[PF₆]⁻ 1a and 1-(2-hydroxy-ethyl)-3-methyl-imidazolium tetrafluoroborate [HOC₂mim]⁺[BF₄]⁻ 1b.

Preparation of ionic liquid supported 3-(2-((4-fluoro-3-nitrobenzoyl)oxy)ethyl)-1-methyl-1H-imidazol-3-ium as BF₄ salt

By taking the appropriate amounts of ionic liquid and the 4-fluoro-3-nitrobenzoic acid and the coupling reagent DCC and the cat. Amount of DMAP in a microwave vessel as DCM/CAN is the solvent. The reaction mixture further submitted to the microwave irradiation for about 20 min of reaction time at 100°C of reaction temperature. Then the reaction mixture has been filtered off and the precipitated DCU and the reaction mixture submitted to the rotavapour in order to reduce the solvent. The reaction mixture has been washed several times with the chilled ether then it has been dried to carry out the further steps. The formation of the product has been confirmed by the ¹H NMR spectroscopy (Scheme 1).

Preparation of 1-methyl-3-(2-((4-(substitutedamino)-3-nitrobenzoyl)oxy)ethyl)-1H-imidazol-3-ium as BF₄ salt

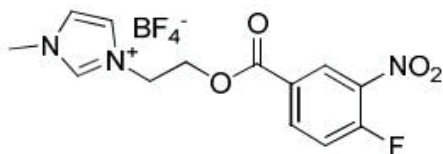
By taking the appropriate amount of ionic liquid substituted 4-fluoro-3-nitrobenzoic acid and the 5.0 eq of aliphatic or the aromatic primary amines in a microwave reaction vessel as the solvent of acetonitrile and then the reaction mixture has been irradiated for about 15 min of reaction time at 80°C of the reaction temperature. After the completion of the reaction the reaction mixture has been submitted to the rotavapour and then the reaction crude washed several times with the chilled ether. The formation of the product has been confirmed by the proton NMR spectroscopy (Scheme 2).

Preparation of the 3-(2-((3-amino-4-(substitutedamino)benzoyl)oxy)ethyl)-1-methyl-1H-imidazol-3-ium as BF₄ salt

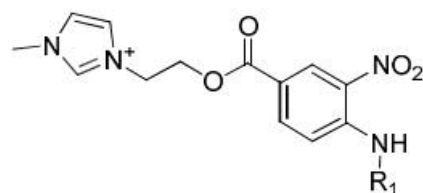
By taking the appropriate amount of the above compound and then the reaction mixture treated with the reducing agent 7.0 eq of Zn and 15.0 eq of ammonium formate to reduce the nitrofunctional group. The reaction mixture was placed in a microwave vessel and irradiated for about 5 min of reaction time at 80°C of reaction temperature. Then the crude reaction mixture washed several times with the chilled ether. Then it has been dried and confirmed by the proton NMR spectroscopy (Scheme 3).

Preparation of 3-(2-((3-(2-cyanoacetamido)-4-(methylamino)benzoyl)oxy)ethyl)-1-methyl-1H-imidazol-3-ium as BF₄ salt

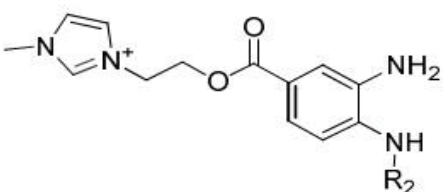
By taking the appropriate amounts of ionic liquid supported diamine and then the cyanoacetic acid in the microwave reaction vessel and the coupling reagent DCC and the catalytic amount of DMAP allowed to stir at room temperature; and then subjected to the microwave irradiation for about 15 min of reaction time at 120°C of reaction temperature. Then the reaction mixture subjected to the rota



Scheme 1: 3-(2-((4-fluoro-3-nitrobenzoyl)oxy)ethyl)-1-methyl-1H-imidazol-3-ium.



Scheme 2: 1-methyl-3-(2-((4-(substitutedamino)-3-nitrobenzoyl)oxy)ethyl)-1H-imidazol-3-ium.



Scheme 3: 3-(2-((3-amino-4-(substitutedamino)benzoyl)oxy)ethyl)-1-methyl-1H-imidazol-3-ium.

evaporator and then crude reaction mixture washed several times with the chilled ether. Then the reaction product has been confirmed by the ^1H NMR spectroscopy (Scheme 4).

Preparation of 3-(2-((2-(cyanomethyl)-1-methyl-1H-benzo[d]imidazole-5-carbonyl)oxy)ethyl)-1-methyl-1H-imidazol-3-ium as BF_4 salt

The above obtained above compound has been placed in a microwave reaction vessel and then it has been added by the solution of 10% TFA in EDC solution, subjected to microwave irradiation for 15 min of reaction time. Then the reaction mixture has been washed several times with the chilled ether and dried for the further scaffold preparation (Scheme 5).

Preparation of methyl 1-methyl-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate

By taking the benzimidazole tethered cyanoacetic acid in the microwave vessel and it has been added the ortho hydroxyl benzaldehyde and the appropriate amounts of triethylamine and the reaction mixture allowed microwaving irradiation for about 15 min of reaction time at 120°C reaction temperature methanol as a solvent. The presence of methanol solvent under organic base condition the ionic liquid will be removed from the scaffold compound. After completion of the reaction the reaction solution has been washed several times with the chilled ether. And then the crude sample subjected to the column chromatography in order to isolate the final scaffolds. Further the same reaction under NaOMe reaction conditions given the better traceless reaction yields (Scheme 6).

Methyl 1-isobutyl-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate

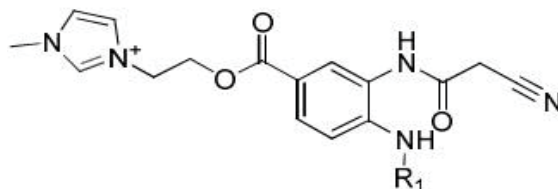
^1H NMR (300 MHz, CDCl_3) δ 8.52 (d, $J=0.7$ Hz, 1H), 8.36 (s, 1H), 8.06 (dd, $J=8.6, 1.35$ Hz, 1H), 7.70-7.63 (m, 1H), 7.47-7.35 (m, 1H), 4.09 (d, $J=7.7$ Hz, 2H), 3.92 (s, 3H), 2.12 (p, $J=6.8$ Hz, 1H), 0.78 (d, $J=6.6$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.4, 158.8, 154.4, 147.4, 142.0, 133.4, 129.0, 125.1, 124.8, 122.3, 118.5, 116.9, 110.4, 52.7, 52.2, 33.8, 28.9, 24.9, 20.0. MS (ESI): m/z 377.0 ($\text{M}+\text{H}$) $^+$; HRMS (ESI): calculated for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4$: m/z 376.4052; Found 377.0 ($\text{M}+\text{H}$) $^+$; IR(neat): 2958, 1718, 1608 cm^{-1} (Scheme 7). Yield 75%.

Methyl 1-butyl-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate

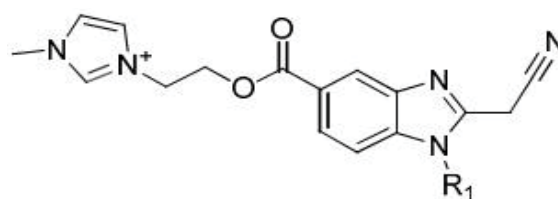
^1H NMR (300 MHz, CDCl_3) δ 8.51 (d, $J=1.1$ Hz, 1H), 8.33 (s, 1H), 8.06 (dd, $J=8.6, 1.56$ Hz, 1H), 7.69-7.62 (m, 2H), 7.48-7.36 (m, 2H), 4.26 (d, $J=7.5$ Hz, 2H), 3.93 (s, 3H), 1.81 (p, $J=7.6$ Hz, 1H), 1.26 (sex, $J=7.7$ Hz, 2H), 0.87 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.9, 159.4, 157.4, 154.8, 150.2, 147.8, 142.9, 139.3, 136.2, 134.8, 133.8, 130.2, 129.4, 125.6, 125.2, 125.1, 123.4, 122.9, 119.5, 118.9, 117.2, 110.6, 52.6, 45.8, 34.3, 32.0, 25.3, 20.5, 13.9; MS (ESI): m/z 377.1 ($\text{M}+\text{H}$) $^+$; HRMS (ESI): calculated for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4$: m/z 376.4052; Found 377.1 ($\text{M}+\text{H}$) $^+$; IR(neat): 2952, 1718, 1608 cm^{-1} (Scheme 8). Yield 80%.

Methyl 2-(2-oxo-2H-chromen-3-yl)-1-phenethyl-1H-benzo[d]imidazole-5-carboxylate

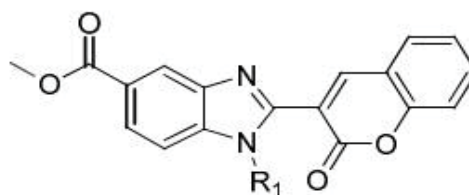
^1H NMR (300 MHz, CDCl_3) δ 8.51 (d, $J=0.9$ Hz, 1H), 8.11 (dd, $J=8.5$ Hz, xH), 7.63-7.50 (m, 1H), 7.41-7.29 (m, 2H), 6.95 (t, $J=3.5$ Hz, 1H), 4.26 (d, $J=7.5$ Hz, 2H), 3.93 (s, 3H), 1.81 (p, $J=7.6$ Hz, 1H), 1.26 (six, $J=7.7$ Hz, 2H), 0.87 (t, $J=7.3$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ



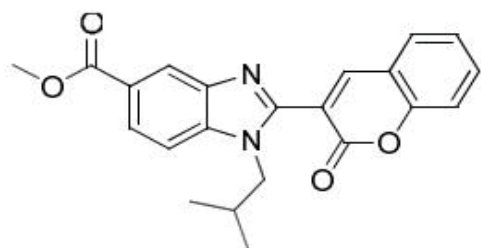
Scheme 4: 3-(2-((2-(2-cyanoacetamido)-4-(methylamino)benzoyl)oxy)ethyl)-1-methyl-1H-imidazol-3-ium.



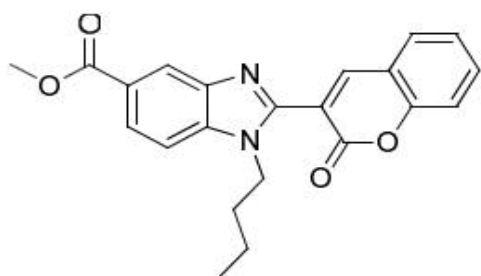
Scheme 5: 3-(2-((2-(cyanomethyl)-1-methyl-1H-benzo[d]imidazole-5-carbonyl)oxy)ethyl)-1-methyl-1H-imidazol-3-ium.



Scheme 6: methyl 1-methyl-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate.



Scheme 7: Methyl 1-isobutyl-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate.



Scheme 8: Methyl 1-butyl-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate.

167.4, 166.9, 158.9, 154.1, 150.2, 148.5, 146.6, 142.5, 138.4, 137.8, 133.0, 128.9, 128.8, 128.5, 127.1, 124.9, 122.5, 118.5, 117.9, 116.6, 109.9, 52.2, 47.1, 35.3; MS (ESI): m/z 425.2 (M+H)⁺; HRMS (ESI): calculated for C₂₆H₂₀N₂O₄; m/z 424.4480; Found 425.2 (M+1)⁺; IR (neat): 2925, 1718, 1608 cm⁻¹ (Scheme 9). Yield 85%.

Methyl 1-(2-(cyclohex-1-en-1-yl)ethyl)-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate

¹H NMR (300 MHz, CDCl₃) δ 8.50 (d, J=1.0 Hz, 1H), 8.32 (s, 1H), 8.1 (dd, J=1.4, 8.5 Hz, 2H), 7.67-7.59 (m, 1H), 7.48-7.34 (m, 2H), 5.17 (s, 1H), 4.35 (t, J=7.2 Hz, 2H), 3.95 (s, 3H), 2.39 (t, J=7.2 Hz, 2H), 1.92-1.87 (m, 2H), 1.80-1.78 (m, 4H), 1.43-1.33 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 167.5, 158.9, 154.4, 149.8, 147.4, 142.4, 133.4, 133.3, 128.9, 125.2, 124.8, 124.7, 124.5, 122.4, 119.1, 118.5, 116.8, 110.2, 52.1, 49.1, 44.4, 37.6, 33.8, 32.5, 28.2, 25.5, 25.0, 24.8, 22.5, 21.8; MS (ESI): m/z 429.1 (M+H)⁺; HRMS (ESI): calculated for C₂₆H₂₄N₂O₄; m/z 428.4798; Found 429.1 (M+1)⁺; IR (neat): 2925, 1718, 1608 cm⁻¹; yield 80% (Scheme 10).

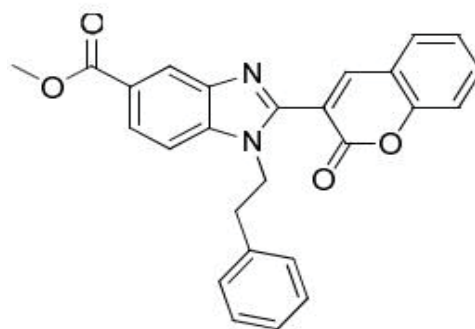
Methyl 1-cyclooctyl-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate

¹H NMR (300 MHz, CDCl₃) δ 8.50 (s, 1H), 8.28 (s, 1H), 8.02 (dd, J=1.4, 8.6 Hz, xH), 7.66-7.55 (m, 1H), 7.47-7.31 (m, 2H), 4.47-4.46 (m, 1H), 3.95 (s, 3H), 2.45-2.34 (m, 4H), 2.18-2.04 (m, 4H), 1.93-1.79 (m, 4H), 1.70-1.52 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ MS (ESI): m/z 452.2 (M+Na)⁺; HRMS (ESI): calculated for C₂₆H₂₆N₂O₄; m/z 430.4956; Found 452.2 (M+Na)⁺; IR (neat): 2923, 1716, 1608 cm⁻¹. Yield: 81%.

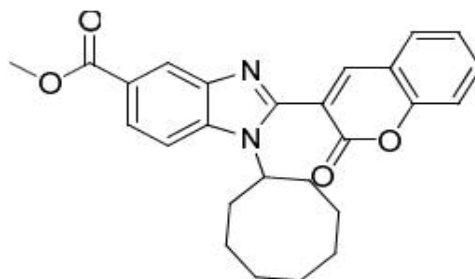
Results and Discussion

By taking the 3-methylimidazole into the reaction vessel; it has been added by the 1.0 equivalence of bromoethanol in sufficient amount of methanol. This reaction mixture has been allowed to the reflux conditions for about 12 hours and then the reaction mixture cooled down to the room temperature and the solution allowed to stir in the room temperature for about 24 hours and the reaction mixture subjected to the Rota vapor in order to remove the methanol solvent.

After the solvent evacuated the crude mixture has been appeared to look like a salt. This salt has been washed several times with diethylether in order to remove the rest of bromoethanol present in the reaction crude; after several times washed with the ether solvent the crude has been subjected to the high pressure vacuum. By taking the sample of the diethyl amine based liquid form ionic liquid and the 2.0 equivalence of 4-Fluoro-3-nitro-benzoic acid and the corresponding amount of coupling reagent DCC and the catalytic amount of DMAP has been taken into the microwave reaction vessel in the acetonitrile as solvent. The reaction mixture has been allowed to stir at room temperature for about 10 hours and then the reaction mixture has been subjected to the microwave irradiation for about 10 min of reaction time at 80°C of temperature. The reaction crude has been filtered through the filter paper in order to remove the undissolved DCU in the reaction mixture. After that the reaction mixture has been subjected to the rotavapor and the solvent residues are removed. The obtained crude product has been washed several times with the diethyl ether until the product has been precipitated. The precipitated product has been dissolved into the acetonitrile solvent and the various ranges of primary and amine has been added to form the nucleophilic substituted products. This reaction has been done at the room temperature conditions for about one hour. Then the reaction crude residue has been subjected to the rotavapor and the obtained crude washed several times with the ethyl ether until the formation of product in the form of precipitation. Then the obtained product has been taken to reduce the nitro functional group in the presence of the reducing reagent. This reaction has been done in the presence of Zn and the ammoniumformate in methanol as a solvent. After the reaction completion the crude has been filtered and the solvent was evacuated. The ammoniumformate was removed by dissolving the crude in the dichloromethane and precipitation. All these subsequent reaction intermediate are taken and submitted to the mass. The mass been matched to the expected value on accurate actual value. There be taking the ionic liquid supported conjugate diamine and the



Scheme 9: Methyl 1-(2-(cyclohex-1-en-1-yl)ethyl)-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate.



Scheme 10: Methyl 1-cyclooctyl-2-(2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-5-carboxylate.

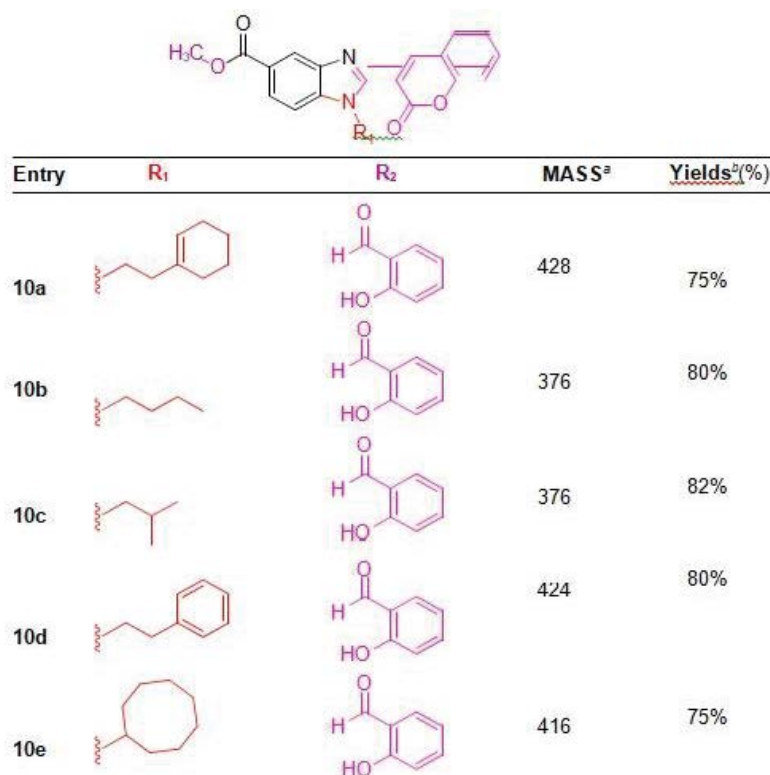


Figure 3: Library of synthetic analogues [10,11].

cyanoacetic acid and to couple with the diamine to acid substrate. This reaction has been done in the presence of DCC as the coupling reagent and catalytic amount of DMAP as the reaction catalyst in acetonitrile in room temperature for about 10 hour of reaction of time. The same reaction was done in the microwave irradiation for about of 10 min of reaction time. The reaction mixture was subjected to the rota vapor to evacuate the acetonitrile solvent. There by the reaction crude has been washed several times with diethyl ether. The obtained substrate has been taken for to generate the benzimidazole attached methyl cyanide substance. This reaction has been done in the presence of 10% of TFA in EDC solvent under reflux conditions for about 10 hours of reaction time. The same reaction was completed in 15 min of reaction under microwave irradiation. After the completion of the reaction the reaction crude has been washed with the diethyl ether for several times. The obtained crude product has taken and added the appropriate amounts of various 2-hydroxy benzaldehyde, 2-aminobenzaldehyde and 2-mercaptobenzaldehyde and the triethylamine in methanol for about of 10 hours of reaction time under reflux condition. The obtained reaction crude has been taken tested for the TLC; then concluded the substrate has been detached from the ionic liquid support to leave the product (Figure 3).

Conclusion

In conclusion we described highly automated multistep procedure polymer-assisted solution phase (PASP) protocols for the synthesis of quinoline, chromene, thiochromen benzimidazol-ylideneamines and benzimidazolones via traceless tandem transformation under microwave irradiation on Ionic strategy with a generic protocol of coupling, detachment, and purification. The synergistic ionic liquid microwave assisted synthesis methodology technology offers several advantages in comparison to the other methods used and developed in

solid- and liquid-phase organic synthesis. First, the attachment of the 4-fluoro-3-nitrobenzoic acid was rapidly performed under microwave irradiation, and the subsequent transformations led intermediates were easily purified by solvent washings. The quantitative transformation of quinoline, chromene, thiochromen benzimidazol-ylideneamines and benzimidazolones via traceless tandem transformation under microwave irradiation into two-component traceless approach because the loading capacity of the hydroxyl functionalized ionic liquids is very high. This method offers the structure and purity of each intermediate could be verified by routine spectroscopic methods. Furthermore, the cost of the starting ionic liquid is probably lower than the solid and liquid support, and in large scale synthesis, this may be an important economic consideration. Although the reaction was accomplished in the homogeneous model, isolation of the desired products as well as ionic liquids could be achieved via a simple filtration, and the TSIL could be reused. This methodology should be compatible with high-throughput liquid-phase organic synthesis and automation technology in regard to the yield of products and emphasizes the green chemistry aspects by avoiding toxic solvents.

Acknowledgements

We gratefully acknowledge National Science Council of Taiwan for the financially supported and the authorities of National Chiao Tung University. Supporting Information Available: The detailed experimental procedures and analytical data (1H, ¹³C NMR, MS, and IR) for all compounds will available free of charge via the Internet at <https://www.pubs.acs.org>.

References

- Elderfield RC (1957) *Heterocyclic Compounds: Six-membered heterocycles containing two hetero atoms and their benzo derivatives*. Wiley.
- Lwowski W, Katritzky AR (1984) *Comprehensive heterocyclic chemistry: the structure, reactions, synthesis and uses of heterocyclic compounds*. Pergamon Press.

- Spasov AA, Yozhitsa IN, Bugaeva LI, Anisimova VA (1999) Benzimidazole derivatives: Spectrum of pharmacological activity and toxicological properties (a review). *Pharmaceutical Chemistry Journal* 33: 232-243.
- Weber J, Antonietti M, Thomas A (2007) Mesoporous poly(benzimidazole) networks via solvent mediated templating of hard spheres. *Macromolecules* 40: 1299-1304.
- Soula C, Luu-Duc C (1986) L'apport des dérivés du benzimidazole en chimie thérapeutique. *Lyon Pharmaceutique* 37: 297-302.
- Rastogi R, Sharma S (1983) 2-Aminobenzimidazoles in organic syntheses. *Synthesis*, pp: 861-882.
- Zou R, Ayres KR, Drach JC, Townsend LB (1996) Synthesis and antiviral evaluation of certain disubstituted benzimidazole ribonucleosides. *Journal of Medicinal Chemistry* 39: 3477-3482.
- Gudmundsson KS, Freeman GA, Drach JC, Townsend LB (2000) Synthesis of fluorosugar analogues of 2, 5, 6-trichloro-1-(β -D-ribofuranosyl) benzimidazole as antivirals with potentially increased glycosidic bond stability. *Journal of Medicinal Chemistry* 43: 2473-2478.
- Zhu Z, Lippa B, Drach JC, Townsend LB (2000) Design, synthesis, and biological evaluation of tricyclic nucleosides (dimensional probes) as analogues of certain antiviral polyhalogenated benzimidazole ribonucleosides. *Journal of Medicinal Chemistry* 43: 2430-2437.
- Hwu JR, Singha R, Hong SC, Chang YH, Das AR, et al. (2008) Synthesis of new benzimidazole-coumarin conjugates as anti-hepatitis C virus agents. *Antiviral Research* 77: 157-162.
- Lee S, Sivakumar K, Shin WS, Xie F, Wang Q (2006) Synthesis and anti-angiogenesis activity of coumarin derivatives. *Bioorganic & Medicinal Chemistry Letters* 16: 4596-4599.
- Neyts J, Clercq ED, Singha R, Chang YH, Das AR, et al. (2009) Structure-activity relationship of new anti-Hepatitis C virus agents: Heterobicyclic-coumarin conjugates. *Journal of Medicinal Chemistry* 52: 1486-1490.
- Velik J, Baliharova V, Fink-Gremmels J, Bull S, Lamka J, et al. (2004) Benzimidazole drugs and modulation of biotransformation enzymes. *Research in Veterinary Science* 76: 95-108.
- Yang EB, Zhao YN, Zhang K, Mack P (1999) Daphnetin, one of coumarin derivatives, is a protein kinase inhibitor. *Biochemical and Biophysical Research Communications* 260: 682-685.
- Thomas JE, Venugopalan M, Galvin R, Wang Y, Bokoch GM, et al. (1997) Inhibition of MG-63 cell proliferation and PDGF-stimulated cellular processes by inhibitors of phosphatidylinositol 3-kinase. *Journal of Cellular Biochemistry* 64: 182-195.
- Fry DW, Bridges AJ, Kraker AJ, McMichael A, Nelson M, et al. (1995) *Assoc Cancer Res* 36: 689.
- Pech R, Böhm R (1984) Synthetic and pharmacologic aspects of thieno structures. *Die Pharmazie* 39: 4-13.
- Fry DW (1996) Recent Advances in Tyrosine Kinase Inhibitors. In: *Annual reports in medicinal chemistry*. Academic Press 31: 151-160.
- Bridges AJ, Zhou H (1997) Synthesis of [1] benzothieno [3, 2-d] pyrimidines substituted with electron donating substituents on the benzene ring. *Journal of Heterocyclic Chemistry* 34: 1163-1172.
- Bilokin YV, Vasylyev MV, Branytska OV, Kovalenko SM, Chernykh VP (1999) A novel and expedient approach to new heterocycles containing benzothiophene, benzothieno [2, 3-d] pyrimidine and coumarin moieties. *Tetrahedron* 55: 13757-13766.
- Boschelli DH, Wu Z, Klutchko SR, Showalter HH, Hamby JM, et al. (1998) Synthesis and tyrosine kinase inhibitory activity of a series of 2-amino-8 H-pyrido [2, 3-d] pyrimidines: identification of potent, selective platelet-derived growth factor receptor tyrosine kinase inhibitors. *Journal of Medicinal Chemistry* 41: 4365-4377.
- Lee SH, Vora J, Lopes de Menezes D, Wiesmann M, Garrett E, et al. (2003) *Proc AACR, 94th AACR Annual Meeting, Washington DC, United States* 44: 934.
- Huang CK, Wu FY, Ai YX (1995) Polyhydroxylated 3-(N-phenyl) carbamoyl-2-iminochromene derivatives as potent inhibitors of tyrosine kinase p60c-src. *Bioorganic & Medicinal Chemistry Letters* 5: 2423-2428.
- Burke Jr TR, Lim B, Marquez VE, Li ZH, Bolen JB, et al. (1993) Bicyclic compounds as ring-constrained inhibitors of protein-tyrosine kinase p56lck. *Journal of Medicinal Chemistry* 36: 425-432.
- Tu NP, Madar DJ, BaMaung NY, Zhou X, Wiedeman PE, et al. (1998) Inhibition of p56 (lck) tyrosine kinase by methyl 3-(N-isothiazolone)-2-thiophenecarboxylate: Structure activity relationship and mechanism of action studies. *The American Chemical Society* 216: U280-U280.
- Ballaron SJ, Sheets M, Mollison KW, Warrior U, Faltynek C, et al. (1997) Irreversible inhibition of p56 (lck) tyrosine kinase by methyl 3-(N-isothiazolone)-2-thiophenecarboxylate. *Infaseb Journal* 11: A1338-A1338.
- Lee SH, de Menezes DL, Vora J, Harris A, Ye H, et al. (2005) In vivo target modulation and biological activity of CHIR-258, a multitargeted growth factor receptor kinase inhibitor, in colon cancer models. *Clinical Cancer Research* 11: 3633-3641.
- Menezes DE, Peng J, Garrett EN, Louie SG, Lee SH, et al. (2005) CHIR-258: a potent inhibitor of FLT3 kinase in experimental tumor xenograft models of human acute myelogenous leukemia. *Clinical Cancer Research* 11: 5281-5291.
- Trudel S, Li ZH, Wei E, Wiesmann M, Chang H, et al. (2005) CHIR-258, a novel, multitargeted tyrosine kinase inhibitor for the potential treatment of t (4; 14) multiple myeloma. *Blood* 105: 2941-2948.
- Murray RD, Mendez J, Brown SA (1982) *The Natural Coumarins, Occurrence, Chemistry and Biology*. John Wiley and Sons, New York.
- Williams JL, Specht DP, Farid S (1998) Ketocoumarins as photosensitizers and photoinitiators. *Polymer Engineering & Science* 23: 1022-1024.
- Spino C, Dodier M, Sotheeswaran S (1998) Anti-HIV coumarins from *Calophyllum* seed oil. *Bioorganic & Medicinal Chemistry Letters* 8: 3475-3478.
- Madhavan GR, Balraju V, Mallesham B, Chakrabarti R, Lohray VB (2003) Novel coumarin derivatives of heterocyclic compounds as lipid-lowering agents. *Bioorganic & Medicinal Chemistry Letters* 13: 2547-2551.
- Kontogiorgis C, Hadjipavlou-Litina D (2003) Biological evaluation of several coumarin derivatives designed as possible anti-inflammatory/antioxidant agents. *J Enzyme Inhib Med Chem* 18: 63-69.
- Hoult JR, Paya M (1996) Pharmacological and biochemical actions of simple coumarins: natural products with therapeutic potential. *General Pharmacology: The Vascular System* 27: 713-722.
- Khan MS, Poonam S (1993) Synthesis of pyranochalcones and related cyclization products. *Indian J Chem B* 32: 817-821.
- Mora A, Paya M, Rios JL, Alcaraz MJ (1990) Structure-activity relationships of polymethoxyflavones and other flavonoids as inhibitors of non-enzymic lipid peroxidation. *Biochemical Pharmacology* 40: 793-797.
- Reutrakul V, Leewanich P, Tuchinda P, Pohmakotr M, Jaipetch T, et al. (2003) Cytotoxic coumarins from *Mammea* harmandii. *Planta Medica* 69: 1048-1051.
- Pochet L, Frédéric R, Masereel B (2004) Coumarin and isocoumarin as serine protease inhibitors. *Current Pharmaceutical Design* 10: 3781-3796.
- Wouters J, Huygens M, Pochet L, Pirotte B, Durant F, et al. (2002) Structural approach of the mechanism of inhibition of α -chymotrypsin by coumarins. *Bioorganic & Medicinal Chemistry Letters* 12: 1109-1112.
- Mor A, Maillard J, Favreau C, Reboud-Ravaux M (1990) Reaction of thrombin and proteinases of the fibrinolytic system with a mechanism-based inhibitor, 3, 4-dihydro-3-benzyl-6-chloromethylcoumarin. *Biochimica et Biophysica Acta (BBA)-Protein Structure and Molecular Enzymology* 1038: 119-124.
- Doucet C, Pochet L, Thierry N, Pirotte B, Delarge J, et al. (1999) 6-Substituted 2-oxo-2 H-1-benzopyran-3-carboxylic acid as a core structure for specific inhibitors of human leukocyte elastase. *Journal of Medicinal Chemistry* 42: 4161-4171.
- Egan D, O'kenney R, Moran E, Cox D, Prosser E, et al. (1990) The pharmacology, metabolism, analysis, and applications of coumarin and coumarin-related compounds. *Drug Metabolism Reviews* 22: 503-529.
- Nicolaidis DN, Fylaktakidou KC, Litinas KE, Hadjipavlou-Litina D (1996) Synthesis and biological evaluation of some 4-(isoxazolonyl or 1, 2, 4-oxadiazolonyl) coumarins. *Journal of Heterocyclic Chemistry* 33: 967-971.
- Tan DS (2005) Diversity-oriented synthesis: exploring the intersections between chemistry and biology. *Nature Chemical Biology* 1: 74-84.
- Thomas GL, Spandl RJ, Glansdorp FG, Welch M, Bender A, et al. (2008) Anti-MRSA agent discovery using diversity-oriented synthesis. *Angewandte Chemie International Edition* 47: 2808-2812.
- Seeberger PH, Danishefsky SJ (1998) Solid-phase synthesis of oligosaccharides and glycoconjugates by the glycal assembly method: a five year retrospective. *Accounts of Chemical Research* 31: 685-695.

48. Plante OJ, Palmacci ER, Seeberger PH (2001) Automated solid-phase synthesis of oligosaccharides. *Science* 291: 1523-1527.
49. Sears P, Wong CH (2001) Toward automated synthesis of oligosaccharides and glycoproteins. *Science* 291: 2344-2350.
50. Jaunzems J, Hofer E, Jesberger M, Sourkouni-Argirusi G, Kirschning A (2003) Solid-Phase-Assisted Solution-Phase Synthesis with Minimum Purification-Preparation of 2-Deoxyglycoconjugates from Thioglycosides. *Angewandte Chemie International Edition* 42: 1166-1170.
51. Seeberger PH, Haase WC (2000) Solid-phase oligosaccharide synthesis and combinatorial carbohydrate libraries. *Chemical Reviews* 100: 4349-4394.
52. Osborn HM, Khan TH (1999) Recent developments in polymer supported syntheses of oligosaccharides and glycopeptides. *Tetrahedron* 55: 1807-1850.
53. Routenberg Love K, Seeberger PH (2004) Automated solid-phase synthesis of protected tumor-associated antigen and blood group determinant oligosaccharides. *Angewandte Chemie* 116: 612-615.
54. Mutter M, Hagenmaier H, Bayer E (1971) New method of polypeptide synthesis. *Angewandte Chemie* 10: 811-812.
55. Bayer E, Mutter M (1972) Liquid phase synthesis of peptides. *Nature* 237: 512.
56. Douglas SP, Whitfield DM, Krepinsky JJ (1991) Polymer-supported solution synthesis of oligosaccharides. *Journal of the American Chemical Society* 113: 5095-5097.
57. Majumdar D, Zhu T, Boons GJ (2003) Synthesis of oligosaccharides on soluble high-molecular-weight branched polymers in combination with purification by nanofiltration. *Organic Letters* 5: 3591-3594.
58. Jiang L, Hartley RC, Chan TH (1996) Use of low molecular weight polyethylene glycol linker for polymer-supported solution synthesis of oligosaccharides. *Chemical Communications*, pp: 2193-2194.
59. Gravert DJ, Janda KD (1997) Organic synthesis on soluble polymer supports: liquid-phase methodologies. *Chemical Reviews* 97: 489-510.
60. Toy PH, Janda KD (2000) Soluble polymer-supported organic synthesis. *Accounts of Chemical Research* 33: 546-554.
61. Miao W, Chan TH (2003) Exploration of ionic liquids as soluble supports for organic synthesis. Demonstration with a Suzuki coupling reaction. *Organic Letters* 5: 5003-5005.
62. Hakkou H, Eynde JJ, Hamelin J, Bazureau JP (2004) Ionic liquid phase organic synthesis (IoLiPOS) methodology applied to the three component preparation of 2-thioxo tetrahydropyrimidin-4-(1H)-ones under microwave dielectric heating. *Tetrahedron* 60: 3745-3753.
63. Yi F, Peng Y, Song G (2005) Microwave-assisted liquid-phase synthesis of methyl 6-amino-5-cyano-4-aryl-2-methyl-4H-pyran-3-carboxylate using functional ionic liquid as soluble support. *Tetrahedron Letters* 46: 3931-3933.
64. Legeay JC, Goujon JY, Vanden Eynde JJ, Toupet L, Bazureau JP (2006) Liquid-phase synthesis of polyhydroquinoline using task-specific ionic liquid technology. *Journal of Combinatorial Chemistry* 8: 829-833.
65. Miao W, Chan TH (2006) Ionic-liquid-supported synthesis: a novel liquid-phase strategy for organic synthesis. *Accounts of Chemical Research* 39: 897-908.
66. Debdab M, Mongin F, Bazureau JP (2006) Ionic-liquid-supported synthesis of amines and derivatives. *Synthesis*, pp: 4046-52.
67. Miao W, Chan TH (2005) Ionic-liquid-supported peptide synthesis demonstrated by the synthesis of Leu5-enkephalin. *The Journal of organic chemistry* 70: 3251-3255.
68. Hu Y, Wei P, Huang H, Han SQ, Ouyang PK (2006) Synthesis of 2-Aminothiophenes on Ionic Liquid Phase Support using the Gewald Reaction. *Synthetic Communications* 36: 1543-1548.
69. Fraga-Dubreuil J, Famelart MH, Bazureau JP (2001) Microwave-assisted oxyhalogenation of carbazole by hydrohalic acids and hydrogen peroxide. 5th Electronic Conference on Synthetic Organic Chemistry (ECSOC-5), Krakow, Poland.
70. Fraga-Dubreuil J, Bazureau JP (2001) Grafted ionic liquid-phase-supported synthesis of small organic molecules. *Tetrahedron Letters* 42: 6097-6100.
71. Fraga-Dubreuil J, Bazureau JP (2003) Efficient combination of task-specific ionic liquid and microwave dielectric heating applied to one-pot three component synthesis of a small library of 4-thiazolidinones. *Tetrahedron* 59: 6121-6130.
72. Arfan A, Bazureau JP (2005) Efficient combination of recyclable task specific ionic liquid and microwave dielectric heating for the synthesis of lipophilic esters. *Organic Process Research & Development* 9: 743-748.