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Research Article

Microwave Assisted Soluble Polymer Supported Synthesis of 7-(1H-Benzoimmidazol-2-yl)-10H-benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2,4-dione

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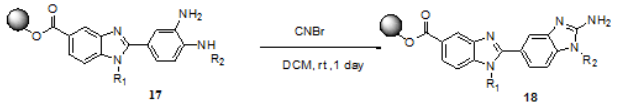
ABSTRACT

Soluble polymer supported bisheterocycles has been synthesized using a convergent synthesis under microwave assisted synthesis. All sequential steps carried out 7 (1 HBenzoimmidazol2yl)10H benzo [4,5] imidazo[1,2-a] [1,3,5]triazine-2,4-dione monitored by the spectroscopic analytical data reported. 4-fluro3-nitrobenzoicacid with various amines nucleophilic substitutions subsequent reduction followed by the acid functional repeated unit of 4 fluro3 nitro benzoicacid heterocyclization lead to the bisheterocyclic scaffold further sequential transformation of nucleophilic substitution with fluoro functional group with various amines followed by reduction of nitro to the amine; to the terminal diamine using cyanobromide leaves bisbenzimidazole with an amine; all steps carried out sing the polymerethleneglycol as support under microwave irradiations all steps compared and analytical spectroscopic data produced. Further under basic conditions bisheteroamine under microwave reaction condition with cloroacetylesters and chloroacetylisocyanates reacts to diamines of benzimidazole with 7-(1H-Benzoimmidazol-2-yl)10H benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2,4-dione. Further under KCN methanol polymer support leaves to molecular scaffolds. A microwave-promoted three-component one pot reaction has been developed to provide access the core 7 (1H Benzoimmidazol 2 yl) 10H benzo [4,5] imidazo [1,2a] [1,3,5] triazine-2,4-dione scaffold, which is common to several families of alkaloids with significant biological activities.

Keywords: Microwave; bisbenzimidazole; chloroacetylesters; chloroacetylisocyanate; cyanobromide; 7-(1H-Benzoimmidazol-2-yl)-10H benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2,4-dione

INTRODUCTION

Microwave-assisted organic synthesis has impacted synthetic chemistry significantly since the introduction of precision-controlled microwave reactors1.



Numerous reactions including heterocycle-forming, metal catalyzed cross-coupling, condensation, and cycloaddition reactions have been explored under microwave conditions2. In addition, microwave-heating technology has been applied in the total syntheses of natural products3. Imidazolin-4-ones (1) constitute an important class of pharmacologically active compounds. The present invention relates to therapeutic compounds and methods of use of these therapeutic compounds for treating cellular proliferative disorders. The invention also provides three-dimensional structures of a Polo-like kinase and methods for designing or selecting small molecular inhibitors using these structures, and the therapeutic use of such compounds. The invention also includes a method for identifying phosphopeptide-binding domains by screening peptide libraries. The carboxy-terminal region of the cell cycle regulating kinase Plk-1 encodes a phosphopeptide recognition domain that consists of the non-kinase region of the protein [1].

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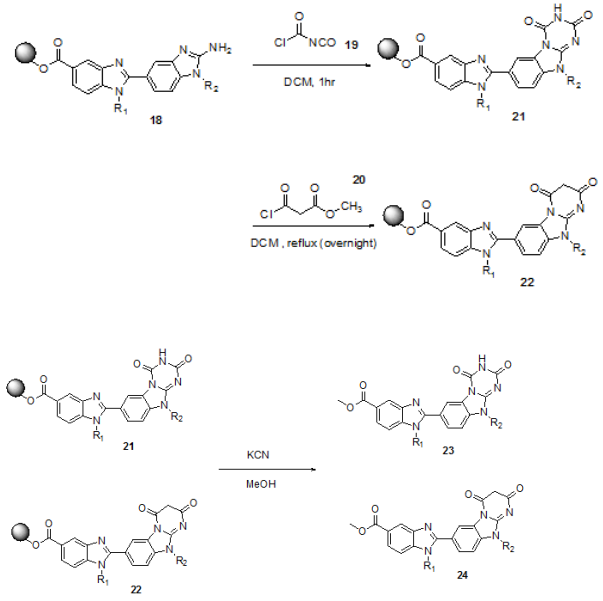


High-content screening has emerged as a new and powerful technique for identifying smallmolecule modulators of mammalian cell biology. The authors describe the development and execution of a high-content screen to identify small molecules thatinduce mitotic arrest in mammalian cancer cells. In this context it should be emphasized that not all micro-wave-assisted reactions proceed to completion within five or ten minutes. In the case of the Liebeskind–Srogl coupling for example, a reaction time of one hour at 130 was required to achieve full conversion and high isolated product yields. The synthesis of a library of thirty compounds using automated sequential processing therefore needed 30 h of processing time. While automated sequential microwave synthesis has been a very successful concept for the construc-tion of small compound libraries, this method may be- come impractical if one considers the generation of larger compound collections since the timesaving aspect of high-speed microwave synthesis is diminished by having to irradiate each reaction mixture individually. In case of the Liebes- kindSrogl reaction, the same dihydropyrimidine librarycould also be synthesized in a parallel microwave fashion producing similar individual product yields in one singleirradiation experiment employing a larger microwave reactorin combination with a multivessel rotor system. Parallel microwave synthesis under controlled conditions can be carried out in a variety of formats, including the use of microtiter plates allowing the simultaneous processing of 200 or more individual microwave reactions. While short reaction times are generally considered as a valuable—but not essential—feature in organic chemistry, they are an indispensable requirement for the synthesis of short-lived radiolabelled (for exampleF) substances used in the field of positron emission tomography (PET).Several research groups have exploited high-speed microwave chemistry for the synthesis of a variety of different radiotracer materials [2-5].

RESULTS AND DISCUSSION

Polyethylene glycol using as support to the 4-floro-3-nitrobenzoicacid starting material to the synthesis of bisbenzimidazole analogues; the coupling with the support done using DCC/DMAP under dichloromethane for about 20 minute reaction under microwave reaction condition under appropriate 120C temperature. Later on removed DCU precipitate out in diethyl ether. To the extent starting material various amines are used nucleophilic substitutions on aromatic benzene ring under microwave reaction condition for about 20 minute 150C; later on washed and precipitated in diethyl ether. Further nitro functional group reduced to the amine under Zn/NH4COOH, methanol at room temperature reaction condition. Further the reaction mixture precipitated from diethyl ether. To the reaction mixture the repeating unit for the bis benzimidazol 4-floro-3-nitrobenzoicacid under DCC/DMAP under microwave irradiation for about 20 minutes of reaction temperature 120C to be form amide bond precipitated from the diethyl ether. Further the reaction mixture using the dichloromethane for about 150C using dehydrating agents MgSO4 reaction mixture concentrate to washed from the diethyl ether, all the steps monitored by the spectroscopy to confirm the reaction steps to proceed. Further the reactions as we did above the nucleophilic substitution followed by the reduction of the fluroro and nitro functional groups under the microwave irradiation and said reaction temperatures as mentioned above, the amines includes aromatic, aliphatic, cyclic, acyclic, leaving the peg supported diamine bisbenzmidazol scaffold. Further the reaction mixture of diamine with the cyanobromide for about an one day room temperature reaction temperature to be convert the amine function to the peg supported bisbenzimidazole; the heterocyclisation includes the leaving the HBr byproduct and to the protonation to the maine subsequent cyclization lead to the free amine of bisheterocycle as an starting material to the further fictionalization [6-10].

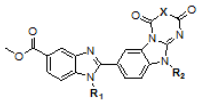


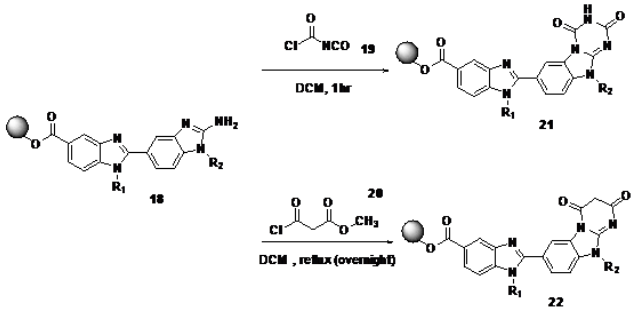
Table 3. 合成7-(1H-Benzoimidazol-2-yl)-10H-benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2,4-dione衍生物

Entry	R_1NH_2	R_2NH_2	X	purity % (b)	LRMS (a)
1			NH	95 %	541(Fab+)
2			NH	86 %	527(Fab+)
3			NH	81%	489(Fab+)
4			NH	74 %	501(Fab+)
5			CH_2	68 %	540(Fab+)

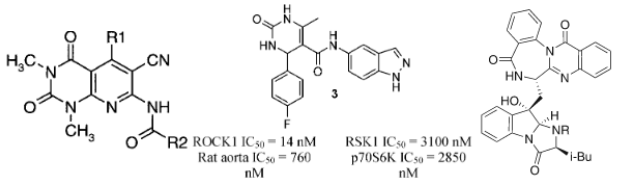
a. mass (M+1) 使用FAB*做为游离源
b. 纯度利用HPLC决定

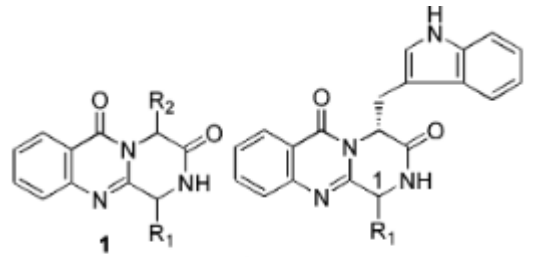
To the polymer supported bisbenzimidazoleamine using an DBU/Et3Nbasic reaction conditions chloroacetylisocyanate for about an 20 minute reaction condition triazinedione

heterocyclisation through the amine condensation observed. The reaction mechanism involves ring amine attacked to the electrophilic carbonyl acid chloride forms the amide further ring emine olefinic bond attackes to the isocyanate carbonyl electrophilic center to form the amide bond leaving the heterocyclisation triazinedione. The same reaction done in microwave for about 20 minutes; the same reaction has done using the acetylchloroester under same reaction conditions for the increase in the diversity in the bis ring scaffold [11-13].



Reaction mixture further precipated from the diethyl ether, all the reaction steps monitored under the spectroscopic studies reported. The entire supported scaffold detached from the support under KCN, methanol to obtain the final compounds to the analytical data.





2, R^1=H, glyantrypine
3, R^1=Me (1S), fumiquinazoline F
4, R^1=Me (1R), fumiquinazoline G
5, R^1=*i*-Pr (1S), fiscalin B

CONCLUSION

In this article, we have described the creation of a well-characterized and lead-like small molecule library as well as acell-based high-content assay to identify compounds that induce mitotic arrest. The high-content assay uses a straightforward and inexpensive DNA stain and a new dataprocessing method, which simplifies data analysis, produces a single scaled measurement per well, and is generally applicable to other high-content assays. The efficient and regioselective construction of 7-(1H-Benzoimmidazol-2-yl)-10H benzo[4,5]imidazo[1,2-a] [1,3,5]triazine-2,4dione and related ring-structures has been shown to be successful even for synthesis of highly polyfunctional. Plants and other natural resources used as traditional medicines have been widely explored in drug discovery. Bioassay directed isolation followed by identification and characterization of bioactive compounds leads a development for new medicinal drugs. Triazine-2, 4dione are one of attractive natural products leading to many drug developments. During the improvement stage of such lead compounds, rational drug design-based modification affords synthetic analogues with increased activity, decreased toxicity, or improved pharmacological availability as exemplified by suggestion of a good candidate as a new antimalarial drug from antimalarial triazine-2,4-dione. From this point of view, simple and convenient method for selective synthesis of compounds such as annelation combined with microwave-assisted synthesis and use of polymer-reagents would be in demand continuously as one of the indispensable strategies for development of new drugs [14-17].

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