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RESEARCH ARTICLE

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Natural Product Inspired Diversity Oriented Synthesis of Tetrahydroquinoline Scaffolds as Antitubercular Agent

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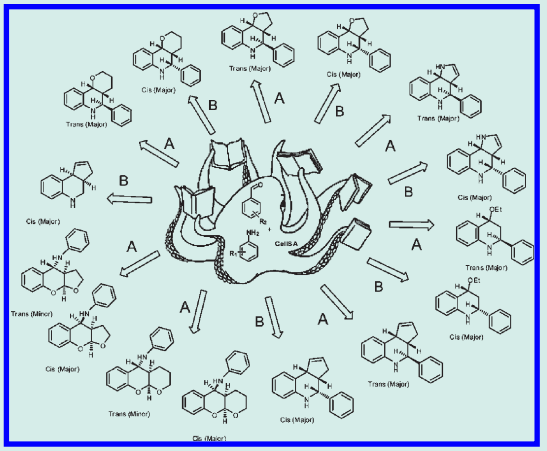
Supporting Information

ABSTRACT: An efficient natural product inspired diversity oriented synthesis of tetrahydroquinoline analogues has been developed using the natural carbohydrate derived solid acid catalyst via multicomponent aza-Diels—Alder reaction of imine (generated in situ from aromatic amine and aldehyde) with dienophile in acetonitrile in a diastereoselective manner. The use of water as solvent reverses the diastereoselectivity toward the cis isomer. Interestingly, tricyclic pyrano/furano benzopyran with cis diastereoselectivity is obtained when salicylaldehyde is used as an alternative of aromatic aldehyde under the same condition. These synthesized quinolines and benzopyrans analogues have been evaluated for their Antitubercular activity against *M. tuberculosis* $H_{37}Ra$, and *M. tuberculosis* $H_{37}Rv$, and some of the analogues shows better activity profile than their natural product analogues. The protocol is not only mild, efficient, ecofriendly, but also involves reusable and biodegradable catalyst and provides route for both the diastereoisomer.



KEYWORDS: natural product inspired synthesis, diversity oriented synthesis, antitubercular agent, tetrahydroquinoline, benzopyran, cellulose sulfuric acid

INTRODUCTION

Mother Nature is about 3.8 billion year old lab which has produced an amazing library of chemical structures unparalleled in number, supreme in diversity and function. These molecular structures are a real treasure and contain diverse information which is encoded in the language of chemistry. Collectively these molecules cover the chemical genome of our planet. With modern knowledge tools in medicinal chemistry we can better use them for the benefit of health. More significantly we can use these resources by making copies of the natural products by doing total synthesis and also by putting the right pharmacophore at the right position for getting more beneficial effects in terms of the biological profile.[1] Natural products always inspired the medicinal chemist for discoveries of new drugs. About 70% of the new chemical entities (NCEs) introduced in the past 25 years were natural products obtained from sources such as plants and animals, derived from natural products, or chemically designed mimics of natural products.[2]

The drug discovery process targeted toward natural products is very tedious, time-consuming, and difficult. The modern drug discovery by applying the tools of synthetic chemistry is an innovative approach, and diversity oriented synthesis has exhibited considerable promise to explore the biologically active chemical space with more density quickly.[3]

Natural products have played a critical role in the identification of several medicines including antibacterial, antifungal, antitubercular, and antitumor compounds.[4] These biologically active heterocycles have been synthesized by total synthesis. Though total synthesis plays a crucial role in the medicinal chemistry efforts,[5] it is time-consuming, impractical, and may lack structural variability. For a lead discovery rationale which is the key of drug discovery, a more rapid solution may be provided by diversity-oriented synthesis (DOS) of natural product-like molecules. A compromise between total synthesis and combinatorial chemistry, DOS concerns molecules displaying sufficient molecular complexity to resemble natural products, but features a more straightforward synthesis, thus allowing introduction of significant structural diversity.[6]

Quinoline alkaloids such as graveolinine, 4-methoxy-2-phenylquinoline, and kokusagine (Figure 1) isolated from Lunasia amara exhibit significant in vitro antitubercular activity against *M. tuberculosis* $H_{37}Rv$.[7] SAR confirmed that the presence of an aryl group, that is, phenyl or a methylenedioxyphenyl ring at the C-2 position, methoxy group at the C-4 position and quinoline nucleus, enhances inhibitory activity. Apart from this, several natural products

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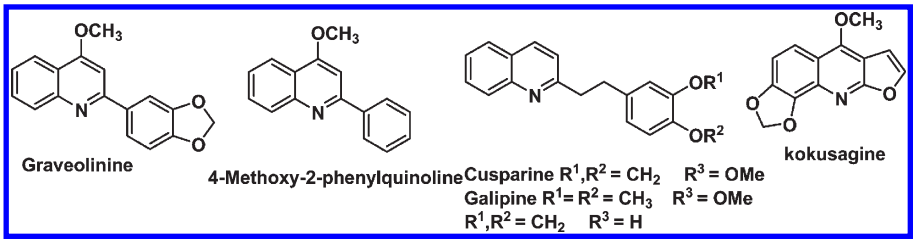

Figure 1. Quinoline Alkaloids exhibiting promising antitubercular activity.

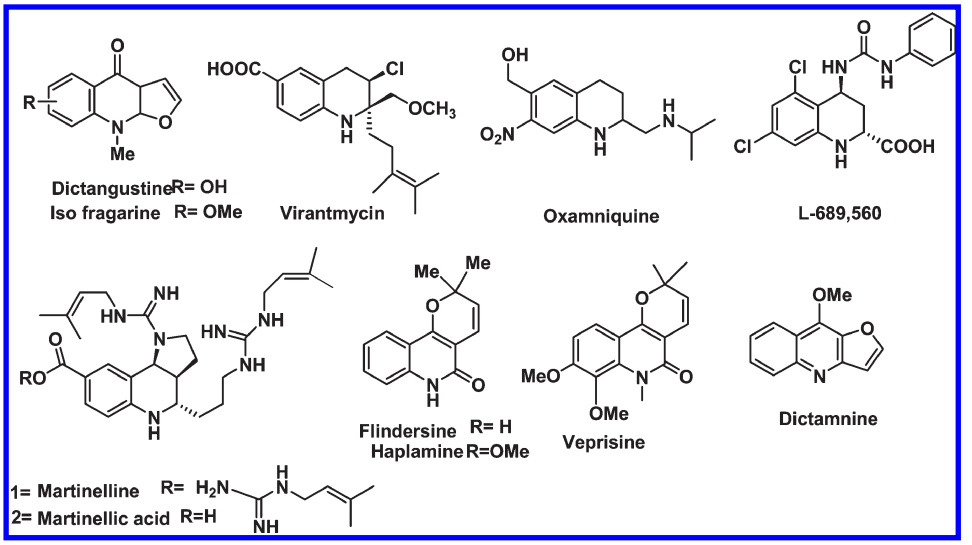

Figure 2. Biologically active quinoline alkaloids.

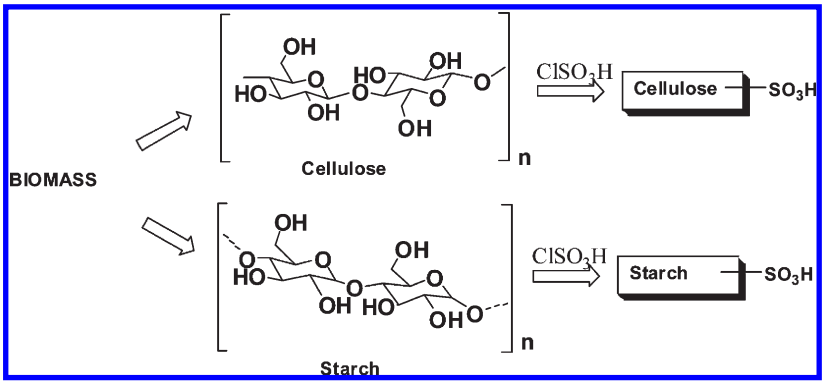

Figure 3. Sulfonated cellulose and starch.

containing tetrahydroquinoline moiety such as martinelline, virantmycin, Oxamniquine, and L-689,560, a very potent *N*-methyl-D-aspartate (NMDA) antagonist (Figure 2) exhibits relevant pharmacological properties.[8]

In continuation of our ongoing research toward the development of diversity oriented or biology oriented synthesis of bioactive analogues with potential pharmacological value[9−11] and inspired from the antitubercular activity of 2-phenylquinoline analogues, we have been interested in designing and synthesizing the diversity oriented 2-phenyl tetrahydroquinoline analogues as an active antitubercular agent. Herein we wish to report an efficient diversity oriented synthesis of antitubercular tetrahydroquinoline via multicomponent synthesis using cellulose sulphuric acid as proton source.

Several synthetic methods have been developed for these compounds,[12,13] among them the aza-Diels−Alder reaction between *N*-arylimine with electron rich dienophile is a powerful method for the construction of tricyclic tetrahydroquinoline ring systems. Since the pioneering work of Povarov,[14] BF_3-OEt_2 has been the most commonly used catalyst for this reaction. However, many of these catalysts are not fully satisfactory with regard to operational simplicity and isolated yield, and some of the previous methods would bring metals or other undesired chemical species into the environment. Hence, there is a quest to find a better and improved methodology for the synthesis of quinoline derivatives.

In view of our ongoing quest for sustainable processes toward the development of environmentally benign synthetic procedures for

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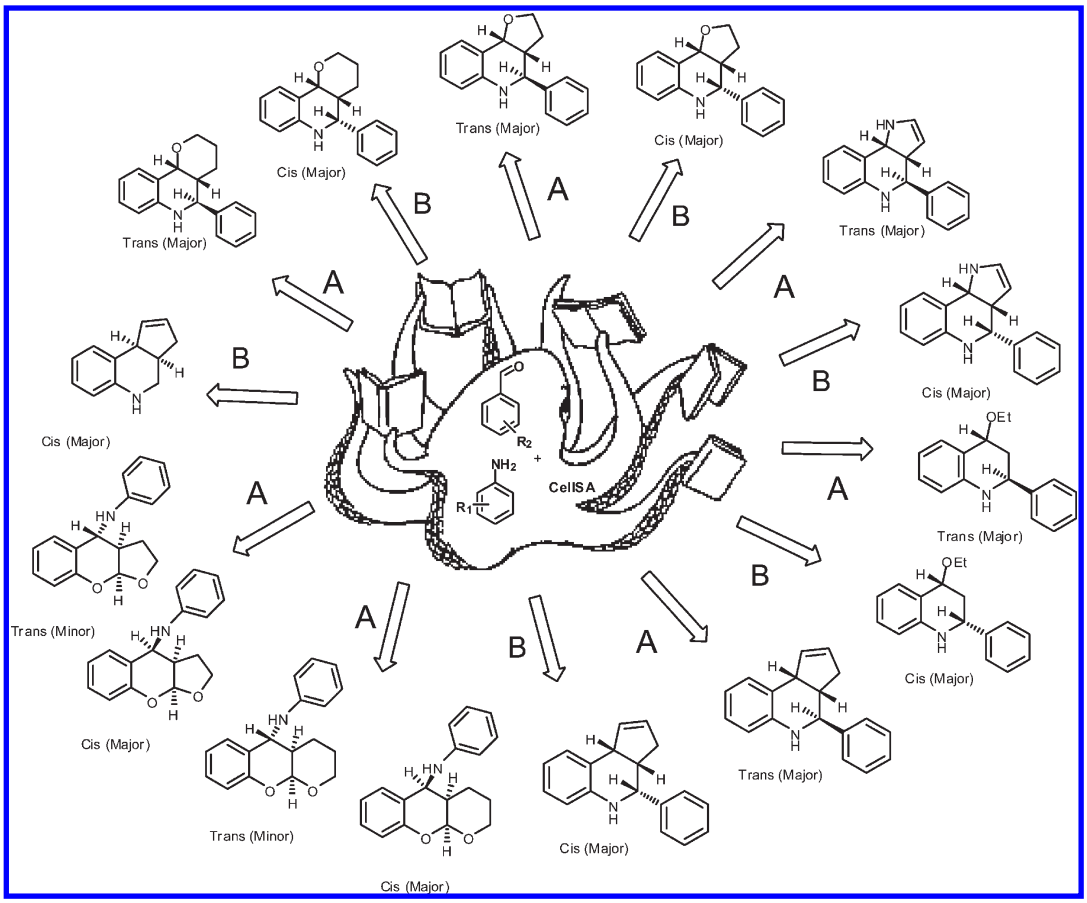


Figure 4. Representative examples of quinolines and benzopyrans prepared using our diversity-oriented synthetic approach using cellulose sulfuric acid, A = Acetonitrile, B = Water.

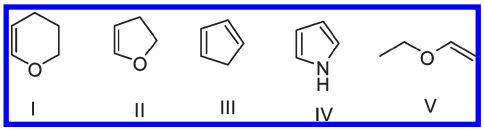


Figure 5. Dienophile used in diversity oriented synthesis of quinolines and benzopyrans.

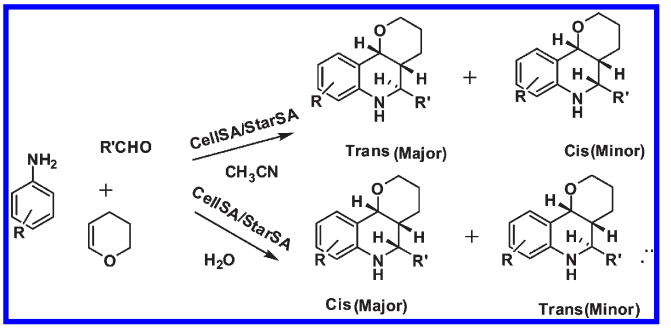
multicomponent reactions,[15] we headed for the development of new ecofriendly catalyst.[16,9c]

Natural biopolymers are attractive candidates in the search for new solid support catalysts.[17] In this regard, the two most abundant natural supramolecular carbohydrates (NSCar), cellulose and starch molecules, are selected for catalytic purposes because these are biodegradable, cost-effective, and obtainable from renewable resources. To accomplish these effective catalytic properties, cellulose and starch were converted to their sulfonic acid derivatives (Figure 3). We have selected sulfonic acid derivatives of carbohydrates as catalyst because many sulfonated active site containing immobilized solid catalyst have exhibited promising results.[18]

RESULTS AND DISCUSSION

In this endeavor we desire to report a facile route for the synthesis of tetrahydroquinoline analogues via Povarov reaction. In the Povarov reaction the in situ generated imines react with a variety of dienophiles yielded a wide range of quinoline heterocycles (Figure 4). The use of cyclic or acyclic enol ethers

Scheme 1. Multicomponent Synthesis of Pyranoquinoline



(Figure 5) greatly improved the molecular diversity of the adduct formed, thereby allowing admittance to diversified tetrahydroquinoline derivatives with considerable biological activities. Therefore, the process is worthwhile for the preparation of libraries of tetrahydroquinoline compounds.

In the Povarov reaction either an aromatic amine, a carbonyl (usually an aldehyde), and an activated olefin react together to yield a tetrahydroquinoline adduct (multicomponent) or an aromatic amine, a carbonyl (usually an aldehyde) react together to form imine, and this in situ form imine reacts with an activated olefin to yield a tetrahydroquinoline adduct (Scheme 1). This stepwise process can be explained mechanistically through the

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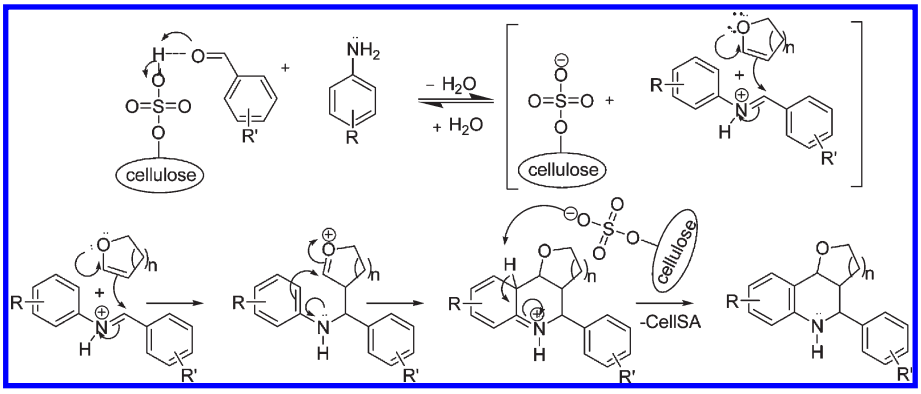

Figure 6. Tentative reaction mechanism for the formation of pyranoquinoline and furanoquinoline.

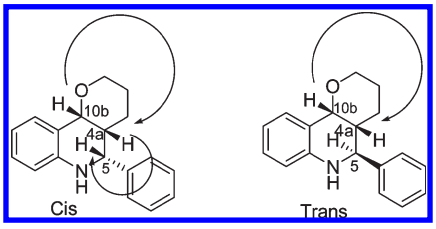

Figure 7. Cis and trans isomer.

generation of an imine, which is attacked by the electron rich nucleophile under acid activation, followed by an intramolecular cyclization (Figure 6).

The diastereoselectivity of quinoline alkaloids strongly depends on solvent. The product was obtained as a mixture of cis and trans isomers. The trans one is formed as the major isomer with organic solvents like acetonitrile. If water is used along with acetonitrile cis selectivity is increased.[19] It is interesting to report here that when water is used as solvent alone, cis isomer was obtained as the major product. The product ratio was determined by ^{1}H NMR spectroscopic analysis. The most diagnostic parameter for the structural assignment is the scalar coupling constant between protons **H-4a** and **H-5**. As depicted in Figure 7, the cis isomer has a small coupling constant ($J_{\text{H-4a, H-5}}$) = 5.0−6.0 Hz consistent with an all *cis* configuration of the hydrogen atoms **4a**, **5**, and **10b**. In the trans isomer, the value of ($J_{\text{H-4a, H-5}}$) = 10.0−11.0 Hz is large and indicative of the antiorientation of protons **H-4a** and **H-5**. The coupling constant ($J_{\text{H-4a, H-10b}}$) in all products (2.2−2.9 Hz) indicates the *cis*- fusion of the pyran- and quinoline rings.[12b]

As an initial stride in the development of the solid acid catalyzed methodology, we tried to prepare tetrahydroquinoline from the reaction of benzaldehyde (1.0 mmol), aniline (1.0 mmol), and 3,4 dihydro-2*H*-pyran (2.0 mmol) as a model in the absence and presence of cellulose and starch sulfuric acid under different temperature conditions (Scheme 1). To optimize the amount of catalyst needed the reaction was carried out by varying amount of the catalyst, and maximum yield was obtained with 0.03 g of catalyst. Further increase in the amount of catalyst in the mentioned reaction did not have any significant effect on the product yield. First, the reaction was carried out with 0.05 g of catalyst, and 60−80% conversion was observed within 2 h at room temperature. Further experiments revealed that even with decreases in the catalyst amount down to 0.03 g, a good conversion (90%) was achieved in 4 h. However, when the catalyst concentration was reduced to 0.01 g, only 35−45% conversion was observed. Thus, using 0.03 g as an optimized catalyst concentration, the reaction time was set up to 2 h. No reaction (NR) took place in the absence of catalyst. Also, with an increase in the temperature (80 °C) no effect on the reaction pace and substrate conversion was noticed; however at room temperature, conversion was cleaner and at 0 °C reaction conversion was much cleaner than at higher temperature. The reusability of the catalyst was also investigated, and it is noteworthy that no obvious decrease in the efficiency was observed for the successive uses of the recovered catalysts.[16]

In this study it was found that cellulose sulfuric acid is a more efficient catalyst over other catalysts with respect to reaction time, yield, and consistency of the desired product. Extending the methodology further similar reaction conditions were also applied on the reaction of benzaldehyde and aniline with 2,3-dihydrofuran, cyclopentadiene, pyrrole, and ethyl vinyl ether. It was observed that 2,3-dihydrofuran, cyclopentadiene, pyrrole, and ethyl vinyl ether show faster reactivity and higher selectivity (because of less steric hindrance of the five membered and acyclic enol ether). Cis and trans compounds produced in similar manner, and trans was the major isomer and cis was the minor isomer when acetonitrile was used as solvent. After the optimized conditions were established, the feasibility of this reaction was examined using several substituted anilines and substituted benzaldehyde. We were pleased to report that in all cases, the reactions gave the corresponding products in good to excellent yield (Table 1). Besides this, unexpected results were obtained when salicyldehyde was used as aromatic aldehyde; in this three-component reaction under same reaction condition functionalized cis-fused *N*-arylamino furanobenzopyrans as a mixture of cis/trans diastereomers was obtained (Scheme 2). In this case cis is the major isomer and trans is the minor one.

Recently, Wang et al. have describe a diastereoselective synthesis of cis-fused pyranobenzopyrans and furanobenzopyrans[20] using preformed *o*-hydroxybenzaldimines with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran. Here one pot multicomponent synthesis of cis-fused furanobenzopyrans using cellulose sulfuric acid is described. To optimize the reaction condition we have performed the reaction of salicylaldehyde and several aromatic amines with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran also. The optimum condition was same as in pyranoquinoline. The corresponding pyranobenzopyrans were obtained as a mixture of cis and trans diastereoisomers in good to excellent yield (54−96%). In most of the cases, the cis isomer was the major product. The ratio of cis and trans isomers was determined from the ^{1}H NMR spectra of the crude products.

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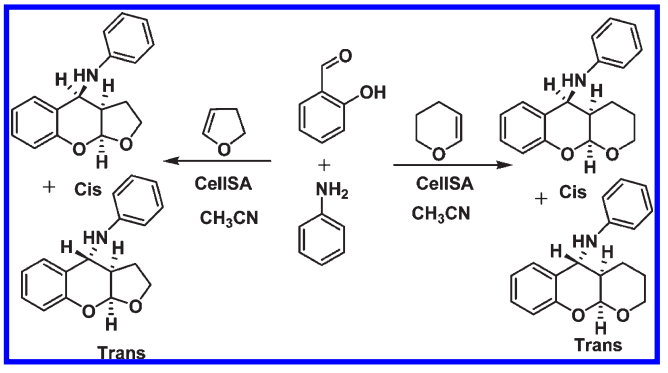
Table 1. Diversity Oriented Synthesis of Tetrahydroquinoline and Benzopyran Derivatives[a,b]

							antitubercular activity-MIC(μg/mL)			
							$H_{37}Ra$[d]		$H_{37}Rv$[e]	
R	(R′-CHO) R′=	dienophile	yield (%)	trans/cis[c](CH_3CN)	cis/trans[c] (H_2O)	time (h)	cis	trans	cis	trans
H	Ph	I	89	65:35	85:15	2.0	12.5	>25	>25	>25
H	2-OCH_3Ph	I	82	59:41	89:11	2.0	25	>25	6.25	>25
Cl	Ph	I	76	55:45	81:19	2.8	12.5	>50	>25	>25
CH_3	Ph	I	75	66:34	88:12	3.5	25	12.5	>25	>25
H	4-OCH_3Ph	I	88	67:33	75:25	3.0	6.25	>25	12.5	>50
H	Ph	II	85	51:49	81:19	3.2	>25	>50	>25	50
H	4-OCH_3Ph	II	89	56:44	76:16	2.5	>25	25	>25	12.5
H	Ph	III	80	69:31	69:31	2.5	>50	nd[f]	>25	nd[f]
4-OCH_3	Ph	III	71	65:35	89:11	2.8	12.5	nd[f]	>25	nd[f]
Cl	Ph	III	83	62:38	72:28	3.0	>25	nd[f]	>50	nd[f]
H	H	III	86	58:42	68:32	3.9	25	>50	≥25	>50
H	Ph	IV	76	52:38	61:49	3.2	>50	nd[f]	>50	nd[f]
H	Ph	V	71	59:41	74:26	2.5	25	>25	25	25
4-OCH_3	Ph	V	80	63:37	79:21	2.5	12.5	nd[f]	12.5	nd[f]
4-Cl	Ph	V	79	55:45	83:17	2.7	25	nd[f]	>25	nd[f]
4-CH_3	Ph	V	64	79:21	76:16	3.0	>25	nd[f]	>25	nd[f]
H	2-OH Ph	II	69	29:71		3.0	>50	>25	>25	12.5
H	2-OH Ph	I	80	35:65		3.8	>25	>50	>25	>50
Kokusagine									16	
Graveolinine									16	

[a] Reaction conditions: aldehyde (5 mmol), aromatic amine (5 mmol), dienophile (10 mmol), CellSA (0.03 g), solvent (CH_3CN/water). [b] All products were characterized by ^1H and ^{13}C NMR spectroscopy. [c] Product ratio was determined from the ^1H NMR spectra of the crude products. [d] MABA MIC (μg/mL) Against *M. tuberculosis* $H_{37}Ra$. [e] Agar micro dilution MIC (μg/mL) against *M. tuberculosis* $H_{37}Rv$. [f] Not determined.

Scheme 2. Multicomponent Synthesis of cis Fused Furano and Pyrano Benzopyran



A plausible mechanistic approach is given in Figure 8. It is proposed that, with *o*-hydroxybenzaldehyde, the reaction probably followed through the formation of an *o*-quinonemethide intermediate, which consequently undergoes cycloaddition with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran leading to the formation of linear pyranobenzopyran and furanobenzopyran, respectively.

All the synthesized compounds were screened for their antitubercular activity using the microalamar blue (MABA) method against *M. tuberculosis* $H_{37}Ra$,[21] while the agar microdilution method was used for the determination of activity against *M. tuberculosis* $H_{37}Rv$.[22] It is interesting to report that some of the synthesized compound show better minimum inhibitory concentrations (MIC) values (6.25 μg/mL and 12.5 μg/mL) in comparison with natural products used for the design, for example, Kokusagine and Graveolinine. The results of antitubercular activity are depicted in Table 1.

CONCLUSION

A diversity-oriented synthetic approach has been developed for the diastereoselective synthesis of tetrahydroquinoline libraries using cellulose sulfuric acid as catalyst which yields skeletally diverse natural product-like compounds. These natural products-like libraries represent an effort to influence the structural features of natural products to target biologically significant regions of chemical structure space. The developed methodology is efficient, and the catalyst used is eco-friendly, reusable, biodegradable, and easily synthesized. We have also reported the synthesis of linear tricyclic pyrano/furano benzopyran with cis diaseteroselectivity using cellSA from salicylaldehyde. These synthesized quinolines and benzopyrans analogues have been evaluated for their antitubercular activity against *M. tuberculosis* $H_{37}Ra$, and *M. tuberculosis* $H_{37}Rv$. We believe this methodology is superior to existing methodologies for the synthesis of both the diastereoisomers of tetrahydroquinolines, which are of immense importance as bioactive molecules.

EXPERIMENTAL SECTION

General Experimental Procedure for the Synthesis of Pyranoquinolines/Furanoquinolines, Cyclopentaquinolines,

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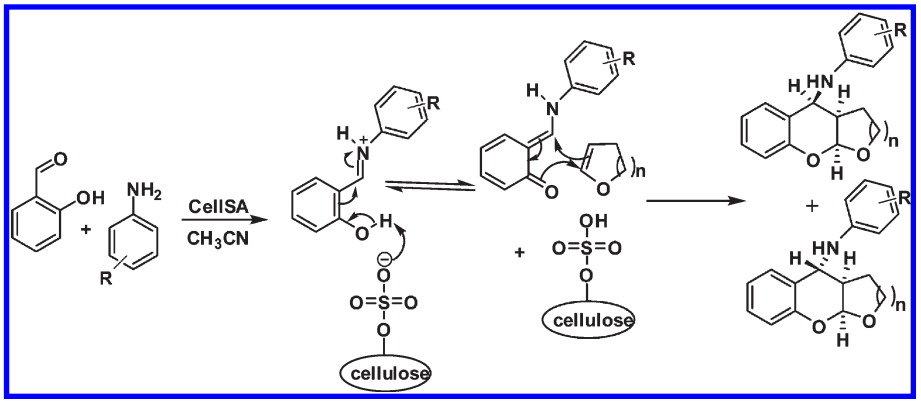

Figure 8. Plausible mechanism for the formation of pyranobenzopyran and furanobenzopyran.

Pyrroloquinolines, 4-Ethoxy-2-phenyl-1,2,3,4-tetrahydroquinoline, cis-Fused Pyranobenzopyrans, and Furanobenzopyrans As Exemplified for Pyranoquinolines/Furanoquinolines. A mixture of aldehyde (5 mmol), aromatic amine (5 mmol), and 3,4-dihydro-2*H*-pyran/2,3-dihydrofuran (10 mmol) was stirred vigorously at 0 °C with cellulose sulfuric acid (0.03 g) in acetonitrile/water (5 mL) for an appropriate amount of time given in Table 1. After completion of the reaction, as indicated on TLC, the reaction mixture was filtered and residue was washed with DCM. The residue containing cellulose sulfuric acid was used for the subsequent reactions. The filtrate was evaporated under reduced pressure to obtain residue. Then water and ethyl acetate was added to the above residue. The organic phase was separated, dried (Na_2SO_4), and filtered and concentrated under vacuum. The crude product was obtained in good yield and purified by column chromatography on silica gel (hexane/EtOAc, 98:2) to separate the cis and trans diastereoisomer.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and compound characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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