The synthesis of chromenes, chromanes, coumarins and related heterocycles *via* tandem reactions of salicylic aldehydes or salicylic imines with α,β-unsaturated compounds

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The tandem reactions of salicylic aldehydes or salicylic imines with α,β-unsaturated compounds have only been studied systematically in recent years. These tandem reactions provide an easy access to a variety of heterocycles, such as chromanes, chromenes, coumarins and tetrahydroxanthenones, many of which are synthetic useful intermediates.

Introduction

Although salicylic aldehydes have been used as substrates in organic synthesis for a long time, attention has only been paid to the tandem reactions of salicylic aldehydes or salicylic imines with α,β-unsaturated compounds in recent years. Different heterocycles, such as chromanes, chromenes, coumarins and tetrahydroxanthenones, were synthesized efficiently through these tandem reactions. As is well known, these heterocycles are widespread elements in natural products and have attracted much attention from a wide area of science, including physical chemistry, medicinal chemistry, natural product chemistry, synthetic organic chemistry and polymer science.[1] Some representative molecules of these heterocycles are shown in Fig. 1.[2] In this paper, we will present a brief review of this area.

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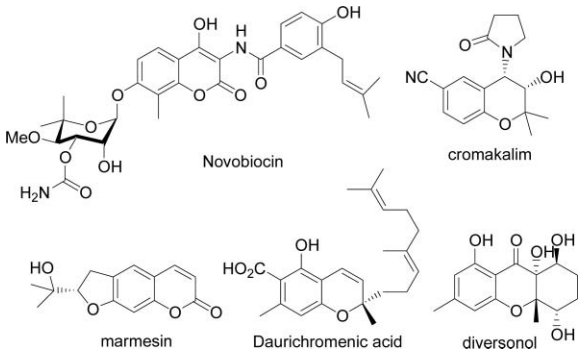

Fig. 1 Some representative molecules.

Reaction of salicylic aldehydes or salicylic imines with acyclic α,β-unsaturated alkenes

In 1982, Kawase *et al.* reported the one-step synthesis of 2,2-dimethyl-2*H*-chromenes by reaction of salicylaldehydes with ethyl

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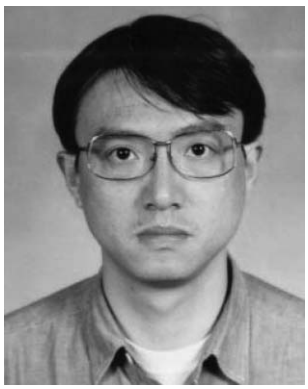

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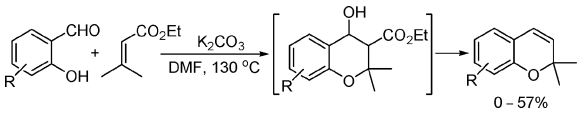
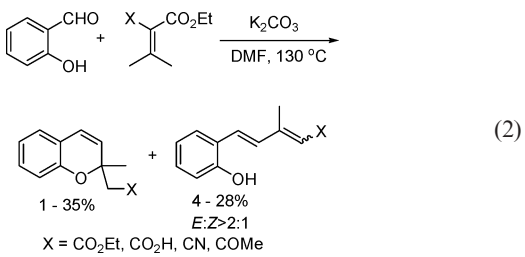
3-methyl-2-butenoate (eqn (1)).[3] Reactions were carried out in DMF at 130 °C and methoxy-, methyl-, chloro-, bromo- and phenyl-substituted salicylaldehydes gave the chromene products in moderate yields, while nitro-, hydroxy-, ethoxy- and acetyl-substituted salicylaldehydes produced poor yields or nothing at all.



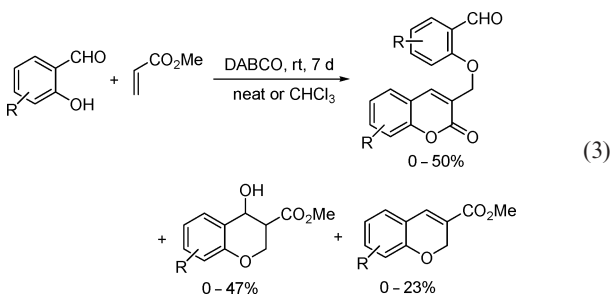
(1)

Later, the condensation of salicylaldehydes with olefins having two electron-withdrawing groups were also reported.[4] The reactions mainly gave polymerized products, and the chromene products were obtained in low yields. Besides the chromene products, some acyclic products were also obtained (eqn (2)).



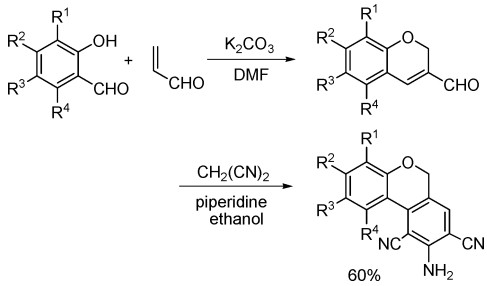
(2)

In 1996, Kaye *et al.* reported the reaction of salicylaldehydes with methyl acrylate to yield three different types of products (eqn (3)).[5] The author proposed that the chromanes, chromenes and coumarins were all derived from the same Baylis–Hillman intermediates, although ^{1}H NMR spectroscopy failed to provide any evidence for the presence of the intermediates. When methyl acrylate was replaced by alkyl vinyl ketones, the corresponding chromenes were obtained in good yields chemoselectively.[6]



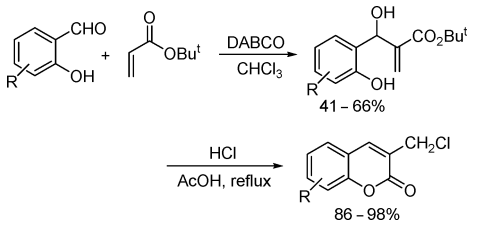
(3)

Subsequently, Ravichandran *et al.* performed the reactions in water.[7] Great rate-enhancement was observed and the reactions were completed within 2 hours, affording the corresponding chromenes in good yields. Later, Kaye *et al.* found that acrylonitrile, acrolein, vinyl ketones, vinyl sulfone and vinyl sulfonate were all suitable activated alkenes for reaction with salicylaldehydes, providing the chromenes in good yields.[8] The chromenes derived from salicylaldehydes and acrolein reacted with malononitrile to give another kind of chromenes in good yields (eqn (4)).[9]



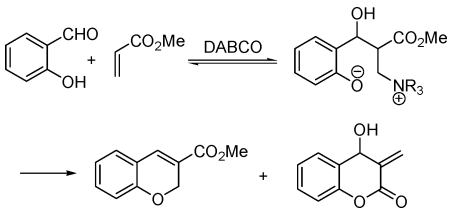
(4)

The reaction between salicylaldehydes and *tert*-butyl acrylate yielded the Baylis–Hillman adducts, which were converted to chromene derivatives by treatment with hydrochloric acid in refluxing acetic acid (eqn (5)).[10]



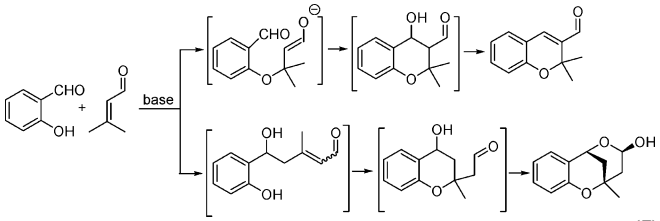
(5)

Kaye subsequently studied the reaction mechanism of salicylaldehyde and methyl acrylate catalyzed by DABCO.[11] The reaction was thought to be initiated by a Baylis–Hillman reaction (eqn (6)). The highly activated dipolar adduct formed by salicylaldehyde, methyl acrylate and DABCO was assumed to be the pivotal intermediate for the formation of chromene and coumarin products.



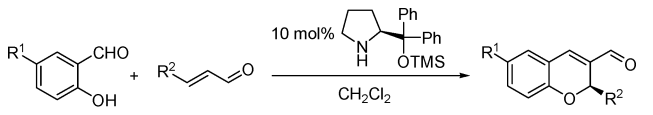
(6)

In 2005, Bräse *et al.* reported the reaction between salicylaldehydes and senecialdehyde systematically.[12] Besides chromenes, tricyclic hemiacetals were also obtained. The mechanism for the reaction is shown in eqn (7). The formation of the tricyclic compound started with the vinylogous addition of the dienolate to salicylaldehyde, followed by a base-promoted intramolecular oxa-Michael addition, then acetalization gave the hemiacetal. The chromene was formed by a tandem oxa-Michael addition, intramolecular aldol reaction and dehydration pathway. The type of catalyst was varied with respect to nucleophilicity and basicity; it was found that sodium carbonate favored the formation of the chromene product and triethylamine favored the formation of the tricyclic hemiacetal.



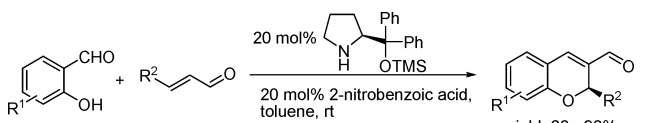
(7)

Very recently, Arvidsson *et al.* reported the first asymmetric version of this transformation using a TMS-protected prolinol derivative as the catalyst (eqn (8)).[13] Several base and acid additives were found to affect both the enantioselectivities and the yields of the product. The more electron-rich 5-methoxy salicylaldehyde resulted in a much faster reaction in higher yield but with lower enantioselectivity. The reaction was thought to proceed by a domino pathway initiated by iminium activation of an α,β-unsaturated aldehyde, followed by intermolecular oxa-Michael addition of a salicylic aldehyde. Then the resulting enamine intermediate underwent an intramolecular aldol reaction and dehydration to give the final chiral chromene product.

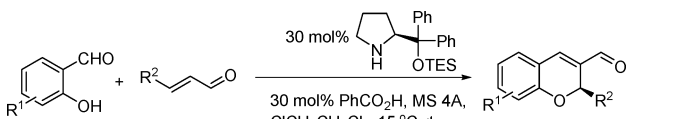


(8)

Similar strategies were also reported independently by Córdova *et al.* and Wang *et al.* Using the same TMS-protected diphenylprolinol as the catalyst, Córdova *et al.* found that the addition of an organic acid increased the enantioselectivity and efficiency of the reaction; 2-nitrobenzoic acid was found to be the best additive. A set of different α,β-unsaturated aldehydes and various salicylaldehydes were all suitable substrates for this reaction (eqn (9)). The yields of the chromene products could be improved without affecting the enantioselectivities by adding molecular sieves (4 Å).[14] Wang *et al.* found that using TES-protected diphenylprolinol as the catalyst could give higher yields of the chromene products (eqn (10)).[15]

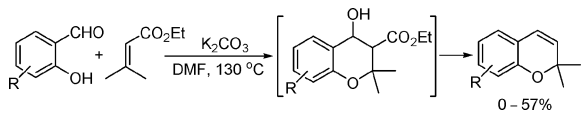


(9)

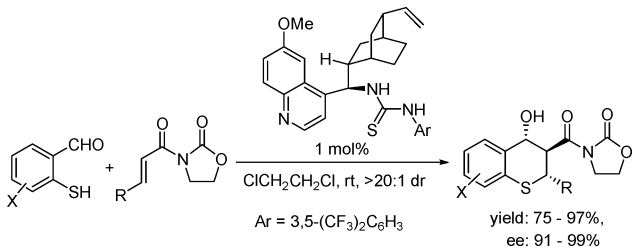


(10)

Wang *et al.* also adopted this approach to synthesize thiochromenes by replacing the phenol group in salicylaldehyde with mercapto group (eqn. 11).[16] Soon after that, similar results were reported by Córdova *et al.* independently.[17] Subseqently, Wang *et al.* used α,β-unsaturated oxazolidinones instead of α,β-unsaturated aldehydes as the Michael acceptors for reaction with 2-mercaptobenzaldehydes. The dehydration process was inhibited and thiochromanes were obtained with high enantio- and diastereoselectivities using 1 mol% of a bifunctional chiral cinchona alkaloid thiourea as the catalyst (eqn (12)).[18]



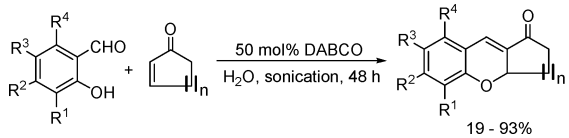
(11)



(12)

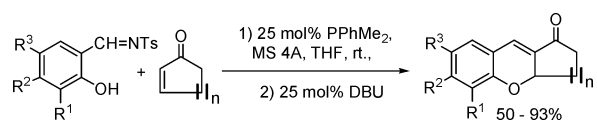
Reaction of salicylic aldehydes or salicylic imines with cyclic α,β-unsaturated alkenes

In 2003, Kim *et al.* and Bräse *et al.* independently reported the reaction between salicylaldehydes and 2-cyclohexen-1-one or 2-cyclopenten-1-one (eqn (13)).[19,20] Using DABCO as the base, the reaction between salicylaldehydes and 2-cyclohexen-1-ones gave the tetrahydroxanthenones in moderate to excellent yields in water with sonication. The reaction was performed with potassium carbonate as a base, while triphenylphosphine, a known catalyst for the Baylis–Hillman reaction, failed to promote the reaction under the same reaction conditions. So an oxa-Michael–aldol reaction–dehydration pathway was proposed, and the derived tetrahydroxanthenone was used for the synthesis of secalonic acids by Bräse *et al.*



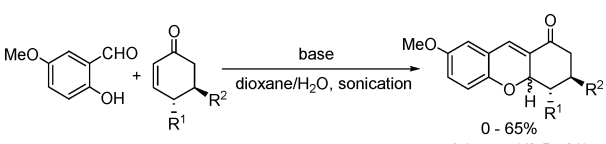
(13)

Subsequently, we found that using salicylic imines instead of salicylaldehydes could shorten the reaction time, and that the reaction was more likely initiated by an aza-Baylis–Hillman reaction (eqn (14)).[21]



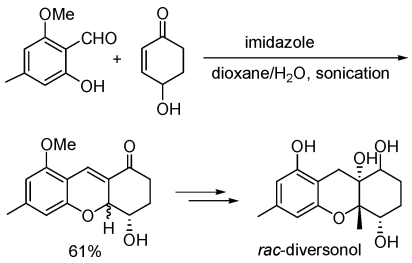
(14)

Later, Bräse *et al.* examined the reactivity of tetrahydroxanthenones and it was found that tetrahydroxanthenones offered various possible further functionalizations, many of which were highly diastereoselective.[22] Bräse *et al.* also investigated the reaction between salicylaldehydes and substituted cyclohexenones (eqn (15)).[23] The reactivity of the cylclohexenones decreases rapidly with increasing steric hindrance around the double bond. The substituent in cylclohexenones at the C-3 position was not tolerated and the substituents at the C-4 or C-5 position were tolerated up to a certain size.



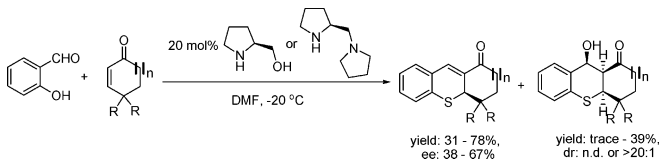
(15)

Bräse *et al.* further used this methodology to achieve the first total synthesis of diversonol in racemic form by transformation of the tetrahydroanthenone derived from a substituted salicylic aldehyde and 4-hydroxycyclohexenone (eqn (16)).[24]



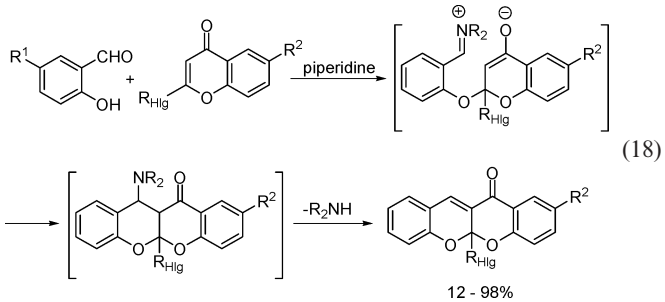
(16)

Córdova *et al.* recently reported the asymmetric synthesis of tetrahydrothioxanthenones through the reaction of 2-mercaptobenzaldehyde with α,β-unsaturated cyclic ketones (eqn (17)).[25]



(17)

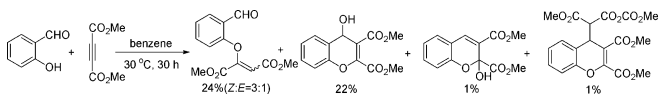
Besides cyclohexenone and cyclopentenone, heterocyclic α,β-unsaturated ketones were also suitable Michael acceptors for reaction with salicylaldehydes. Charushin *et al.* have found that polyhaloalkyl-substituted chromones, γ-pyrones and β-furanones reacted with salicylaldehydes in the presence of piperidine to give fused 2*H*-chromenes in good yields.[26] The reaction was interpreted to follow an oxa-Michael addition–intramolecular Mannich condensation–elimination pathway (eqn (18)).



(18)

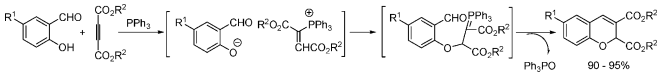
Reactions of salicylic aldehydes or salicylic imines with α,β-unsaturated alkynes

In 1975, George *et al.* reported the reaction between salicylaldehyde and dimethyl acetylenedicarboxylate giving mixtures of chromenes and Michael addition adducts (eqn (19)).[27] Later, they also studied the phototransformations of the chromene derived from salicylaldehyde and diphenyl acetylenedicarboxylate by steady-state and laser photolysis.[28]



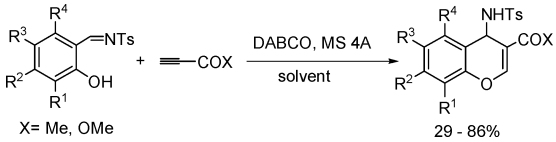
(19)

In 2002, Ramazani *et al.* reported a triphenyl phosphine-mediated reaction between salicylaldehydes and acetylenedicarboxylates, which provided easy access to chromene derivatives.[29] The formation of the chromene product involved the initial addition of triphenylphosphine to the acetylenedicarboxylate and concomitant protonation by salicylaldehyde to form the 1 : 1 ionic pair, followed by attack of the phenolic anion to the vinyl triphenylphosphonium cation, and subsequent cyclization gave the final product (eqn (20)).



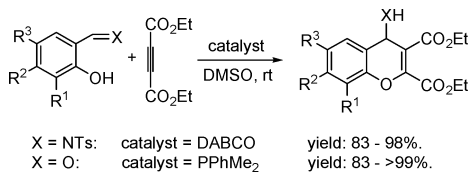
(20)

Very recently, we investigated the reaction between but-3-yn-2-one or methyl propiolate and salicyl *N*-tosylimines.[30] Using DABCO as the catalyt, the reaction yielded highly functionalized chromenes (eqn (21)). The reaction was thought to start with a Michael addition followed by an intramolecular aza-Baylis–Hillman reaction on the basis of ^{1}H NMR spectroscopic investigation during the course of the reaction. The intramolecular aza-Baylis–Hillman reaction was the rate-determining step for this reaction.



(21)

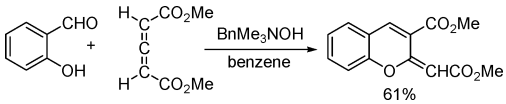
A substituent at the terminal alkyne was not tolerated, presumably due to the steric hindrance. The reaction between ethyl 2-butynoate and salicyl *N*-tosylimine did not give the corresponding chromene derivative in satisfactory yield. Subsequently, we found diethyl acetylenedicarboxylate showed higher reactivity than ethyl 2-butynoate for this reaction.[31] The reactions of salicyl *N*-tosylimines or salicylaldehydes with diethyl acetylenedicarboxylate could proceed under mild conditions giving the corresponding chromenes in excellent yields (eqn (22)).



(22)

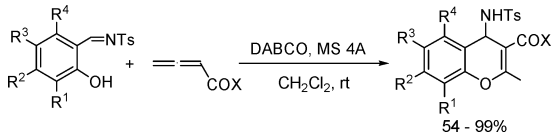
Reaction of salicylic aldehydes or salicylic imines with allenes

In 1983, Scheinmann *et al.* first demonstrated the reaction of dimethyl penta-2,3-dienedioate with salicylaldehyde in benzene in the presence of benzyl trimethylammonium hydroxide to give the chromene (eqn (23)).[32] While after that, the reactions between allenes and salicylaldehydes were less explored.



(23)

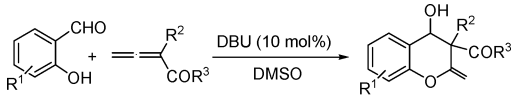
In 2005, we reported the reaction of salicyl *N*-tosylimines with ethyl 2,3-butadienoate or penta-3,4-dien-2-one giving the corresponding chromenes in good to excellent yields, using DABCO as the catalyst in dichloromethane (eqn (24)).[33] Several other catalysts were also examined and it was found that phosphorus-based catalysts, such as PPh_3 or PPh_2Me could induce the reaction to give the [3 + 2] cycloadduct dihydropyrrole derivative with an unreacted phenol group,[34] while the weak nucleophile diisopropyl ethyl amine and inorganic catalysts, such as NaOH, Na_2CO_3, $NaHCO_3$, showed no catalytic activity for this reaction.



(24)

Subsequently, we found that salicylaldehydes could react with 3-methylpenta-3,4-dien-2-one, 3-benzylpenta-3,4-dien-2-one or ethyl 2-methylbuta-2,3-dienoate to give the corresponding functionalized 2*H*-1-chromenes in good to excellent yields and good diastereoselectivities in most of the cases, using DBU as the catalyst in DMSO, but the exact role of DBU and the mechanism for this reaction was not clearly understood (eqn (25)).[35]

Later, the mechanism for this reaction was investigated in detail, and it was found that DBU served as a base for the reaction (eqn (26)).[36]



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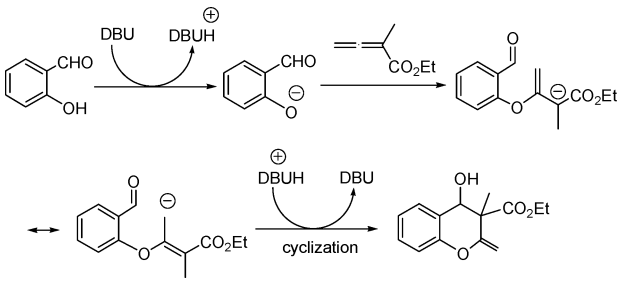
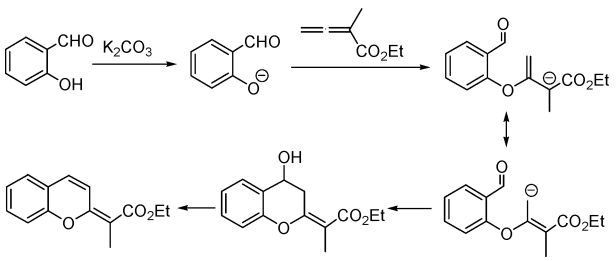


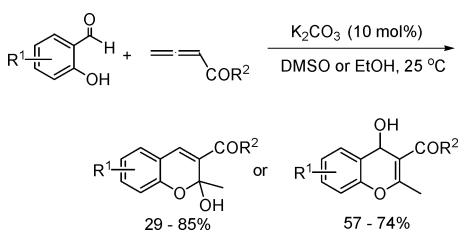
(26)

While using K_2CO_3 as the catalyst at high temperature, the reaction gave another type of chromenes.[37] The mechanism is shown in eqn (27).



(27)

Unsubstituted allenic ketones or esters also reacted with salicylaldehydes using K_2CO_3 as the catalyst at room temperature to give two types of chromenes, respectively, for different salicylaldehydes, and the latter one could be converted to the former one under acidic or neat conditions (eqn (28)).[36]



(28)

Summary and outlook

The reaction of salicylic aldehydes or salicylic imines with α,β-unsaturated compounds provides easy access to different heterocycles, such as chromanes, chromenes, coumarins and tetrahydroxanthenones. In this review, we have outlined some typical work in this area. Although the reactions of salicylic aldehydes or salicylic imines with various α,β-unsaturated compounds have been investigated systematically, further transformation of the products to biologically active compounds is still in its infancy. Future work might be focused on the utilization of these methodologies to synthesize some biologically active molecules or natural products.

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