“Synthesis of resorcinarene macrocontainer for the encapsulation of diclofenac sodium ,and mefenamic acid drugs”

Pharmaceutical Chemistry Department College of pharmacy University of Basrah / Iraq

By student :

Ibrahim Harith

Abstract :

Many drug molecules have low solubility in aqueous media and, hence, poor bioavailability. The formation of a host-guest complex with some other compound which has a good solubility profile. Complex formation relies upon the formation of non-covalent interactions between the host molecule and the drug guest. The use of calix[4] resorcinarene , a well- characterized class of cyclic oligomers, has been investigated for their ability to form complexes with a variety of ionic and molecular species. This study demonstrated the potential of calix[4]resorcinarene as host molecules in novel drug delivery systems.

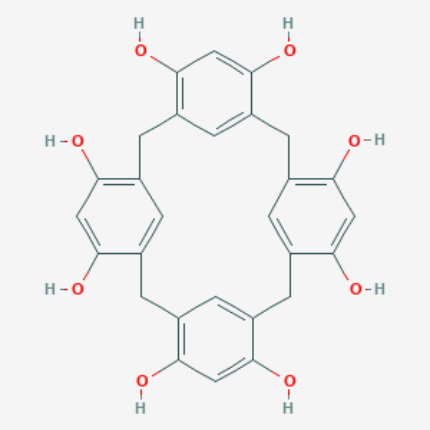
Introduction :

Calix[4] resorcinarenes (or resorcinarenes) are macrocyclic host molecules that possess a bowl-shaped molecular cavity formed by four resorcinol units.These cyclic tetramers are prepared by acid-catalyzed condensation of resorcinol and various aldehydes. Phenolic groups in resorcinarene can be ionized to give anionic have strong affinity for tetra alkyl ammonium ions. Tetra anion of Calix[4]resorcinarenes was found to decrease the hydrolysis of neurotransmitter acetyl choline in the nerves and was also found to bind biologically important tetramethylammonium (TMA) .[1,2,3]

Calix[4]resorcinarenes deliver a versatile molecular platform for the elaboration of more complicated molecular host systems.

Most of reactions with these compounds consists on electrophilic substitution of hydrogen atom between two hydroxyls, or substitutions on hydroxyl groups. One of the easiest reactions is the Mannish-type reaction.

Resorcinarenes serve as host molecules for various metal ions and neutral molecules, and as building blocks for various supramolecular structures such as inclusion complexes, capsules,nanotubes,stationary phase liquid crystals as monolayer formers . [4,5]



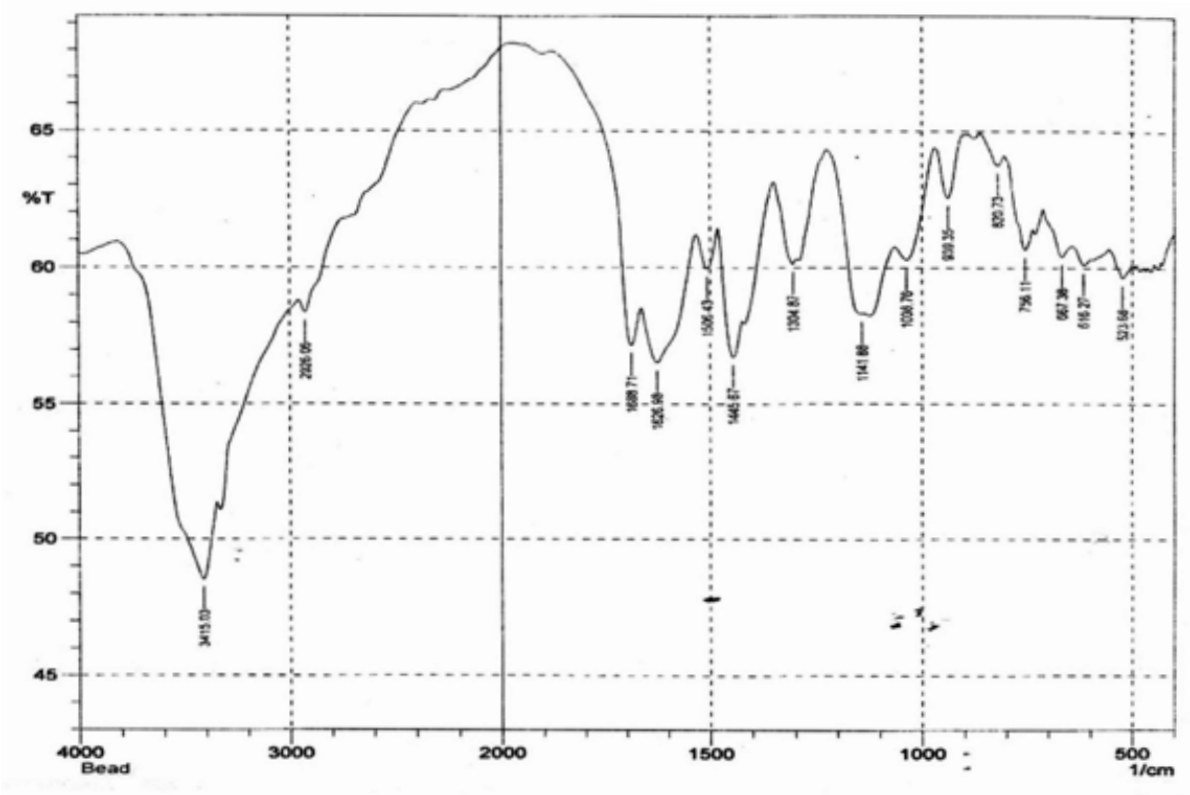
Biocompatibility of calix [4] resorcinarenes :

Biological studies of the toxicity of calix[4] resorcinarenes investigated for clinical use have been reported alongside studies into drug solubilization and other applications. These studies have shown that the calix[4] resorcinarenes are biocompatible with negligible toxicity in vivo. This is obviously critical if they are to be clinically useful in pharmaceutical formulations to enhance drug solubilization and facilitate delivery.[6,7]

Diclofenac sodium :

Diclofenac Sodium is the sodium salt form of diclofenac, a benzene acetic acid derivate and non steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory activity. Diclofenac sodium is a non-selective reversible and competitive inhibitor of cyclooxygenase (COX), subsequently blocking the conversion of arachidonic acid into prostaglandin precursors. This leads to an inhibition of the formation of prostaglandins that are involved in pain, inflammation and fever. [8]

Chemical properties: Crystals , Mp 283 to 285 . Solubility at 25 mg / mL) : deionised water (pH 5 . 2) > 9 ; methanol > 24

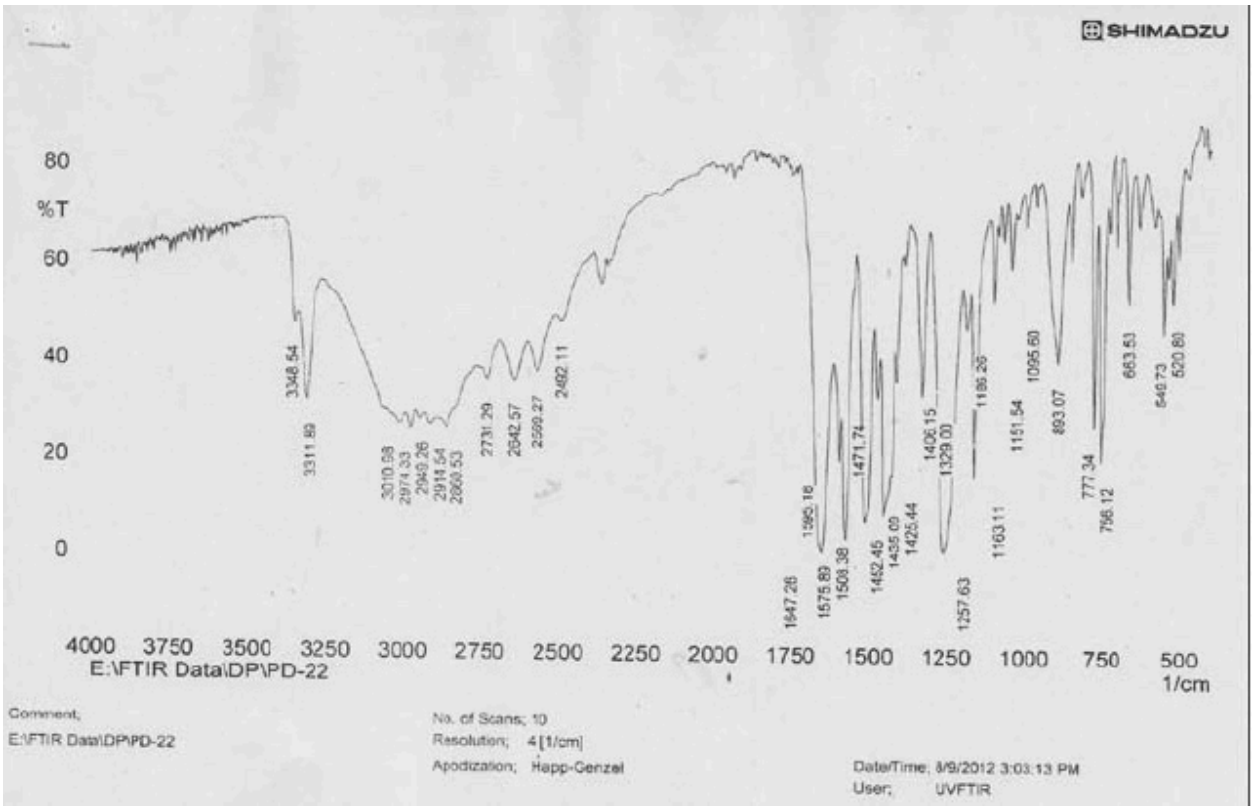


IR spectrum of diclofenac sodium

Mefenamic acid :

Mefenamic acid is a Non steroidal Anti-inflammatory Drug. The mechanism of action of mefenamic acid is as a Cyclooxyrgenase Inhibitor. The chemical classification of mefenamic acid is Non steroidal Anti-inflammatory Compounds. [9]

Chemical Properties: A white to greyish-white microcrystalline powder. Mp 230 to 231, with effervescence. Practically insoluble in water; soluble 1 in 185 of ethanol

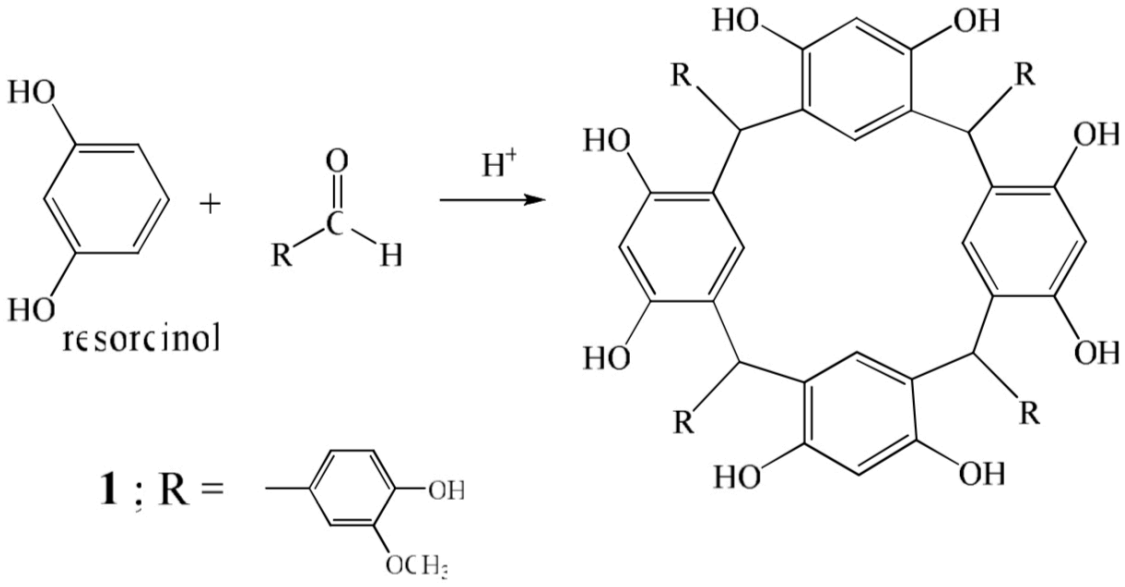


IR spectrum of mefenamic acid

Synthesis of resorcinarene ：

resorcinarene have been synthesized at room temperature under solvent-free condition. This methodology is simple, high-yielding, and energy- efficient which represents a viable alternative to traditional solution phase methodology

The reaction was done according to the method as described by Roberts et al. (2001). A mixture of vanillin , resorcinol , and concentrated acid was added together in a mortar and pestle and ground vigorously. Within seconds, a viscous paste formed which hardened on further grinding. The paste was left to stand for up to 1 h, during which time it solidified to yield a red solid. The solid was reground, washed with water to remove any acid, filtered, and the product was recrystallized with hot methanol to give pink colored solid. [10]



Result and discussion:

First part of result is synthesis of resorcinarene compound by reaction of resorcinol with aldehyde (vanillin) ,the resulted compound is solid red - pink in color .

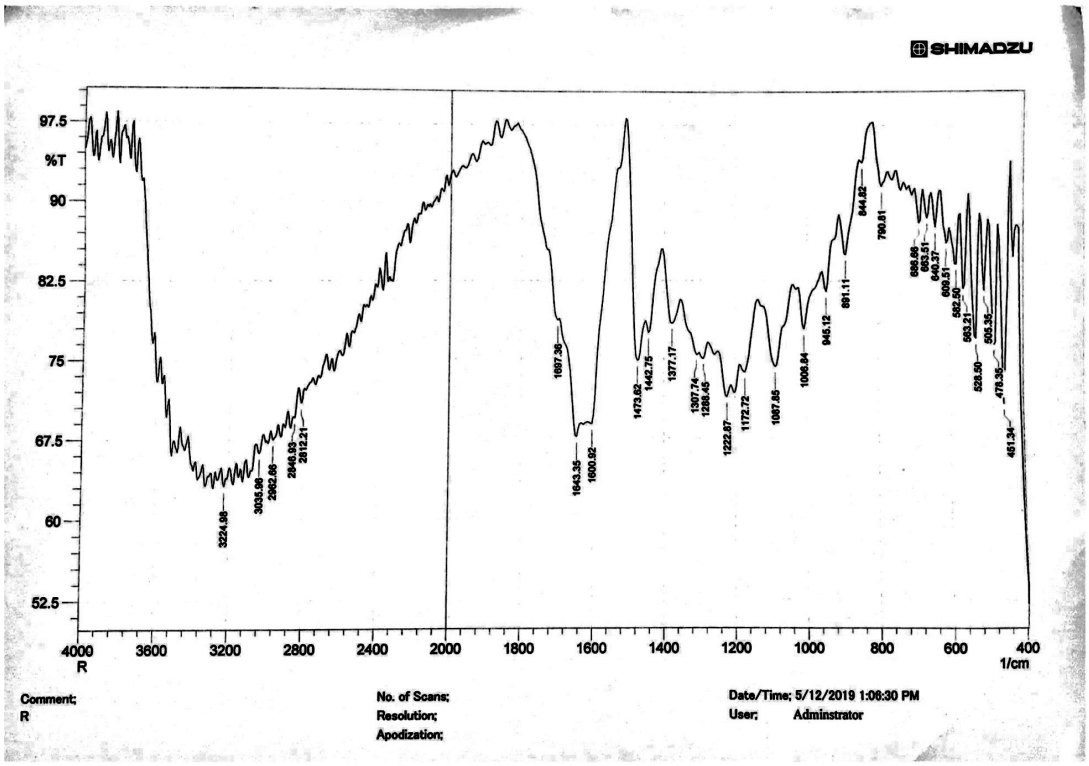
The resulted compound tested by IR spectrophotometer to confirm that the compound is resorcinarene .

The infrared spectra of resorcinarene recorded in KBr phase between 400-4000 cm^{-1}

With Shimadzu IR spectrophotometer

IR spectra show absorption bands for resorcinarene at :

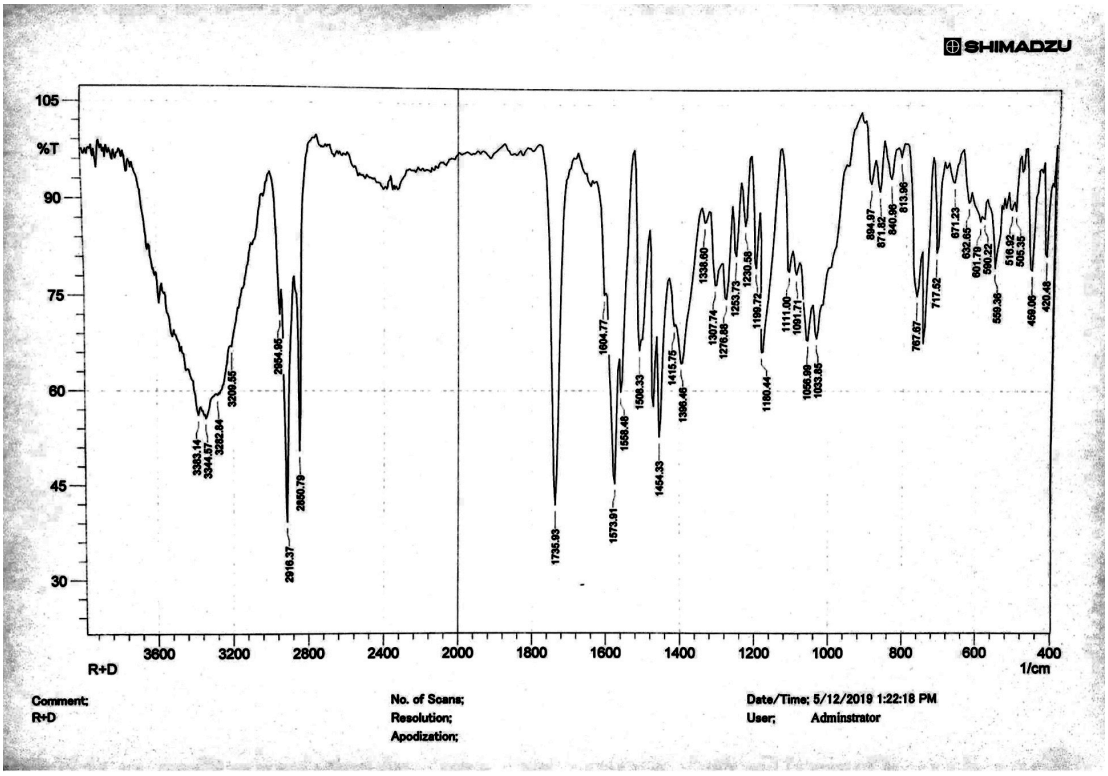
3224 (OH) , 1643,1600 (ArH) , 1473 (-CH) , 3035-2812 (CH_3)



IR SPECTRA OF RESORCINARENE

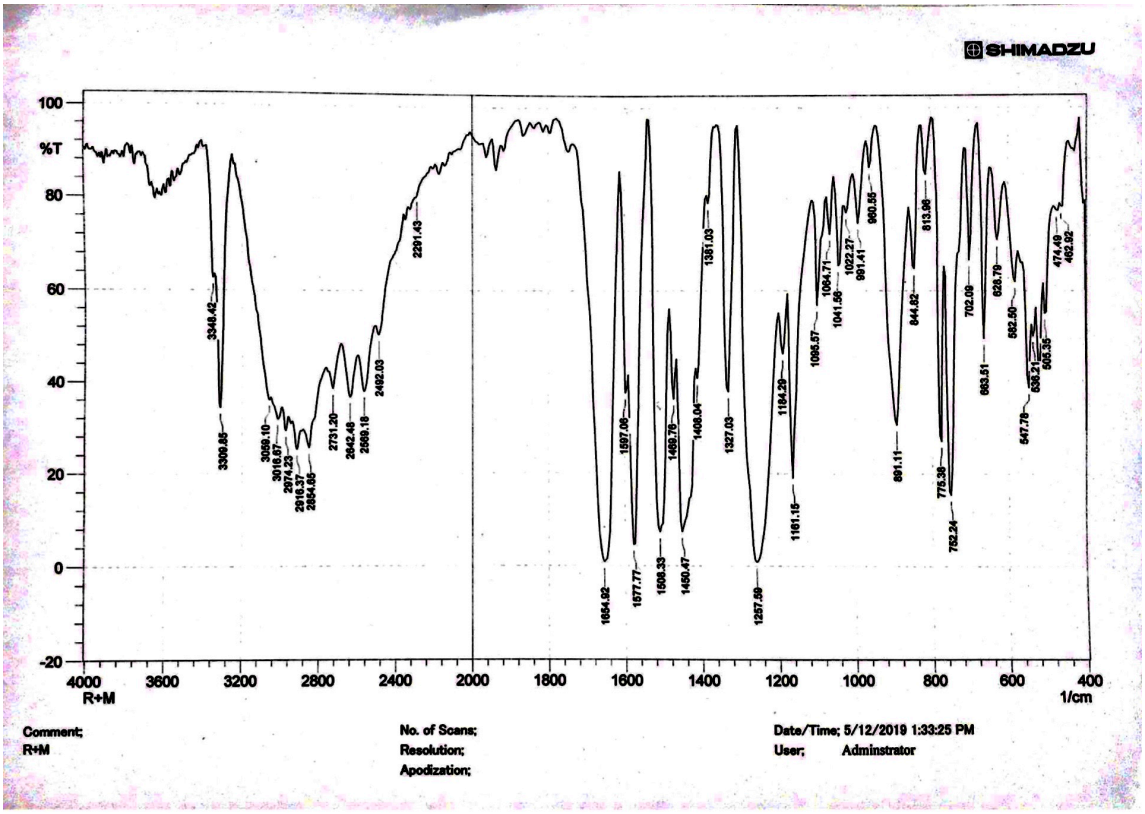
Second part of result is record the IR spectra of Resorcinarene - diclofenac sodium complex and Resorcinarene - mefenamic acid complex to detect any conjugation between them :

If we compare between the IR spectrum for resorcinarene alone and the complex of resorcinarene with diclofenac sodium we can see the broadening of -OH peak disappeared and converted to narrowing peak in the mixture and this refer to a a good conjugation between resorcinarene and diclofenac sodium



IR SPECTRA OF RESORCINARENE AND DICLOFENAC SODIUM COMPLEX

The IR spectra of resorcinarene and mefenamic acid also show some conjugation but less than the conjugation that we get between resorcinarene and diclofenac sodium



IR SPECTRA OF RESORCINARENE AND MEFENAMIC ACID COMPLEX

Conclusion :

In conclusion,water-soluble calix[4]resorcinarene have been demonstrated to improve the solubility of a variety of drug molecules in aqueous media. The reported low toxicity of the calix[4] resorcinarene makes them attractive in comparison to other common solubilizing agents. Complex formation is not simply determined by the chemical and physical properties of the host calix[4]resorcinarene and the guest drug molecule.The various non-covalent interactions that mediate complex formation are influenced greatly by the aqueous environment ,

Future outlook :

calix[4]resorcinarene are increasingly attracting attention in the field of nano science and, hence, nano- medicine. Though the number of reports of the use of resorcinarene in various situations continues to increase the full potential of simple calix[4]resorcinarene for drug solubilization has not been realized. Supramolecular assemblies incorporating calix[4] resorcinarene are attractive to study but it may be argued that the clinical application of these materials may be limited by their complexity.

References :

1. Högberg A. G. S., Two stereoisomeric macrocyclic resorcinol-acetaldehyde condensation products, J. Org. Chem.,
45, 4498 (1980)

2. Mustafina A. R., Elistratova Yu G., Syakaev V.V., Amirov R. R. and Konovalov A. I., Receptor properties of calix[4]resorcinarenes toward tetramethylammonium and choline cations in, micellar solutions of sodium dodecyl sulfate, Russ. Chem. Bull., Int. Ed., 55, 1419 (2006)

3.Schneider H. J., Mechanisms of molecular recognition-Investigations with organic host guest complexes, Angew. Chem. Int. Ed. Engl., 30, 1417 (1991)

4.Cram D. J., Karbach S., Kim Y. H., Baczynskyj L., Marti K., Sampson R. M. and Kalleymeyn G. W., Host-guest complexation, 47, carcerands and carcaplexes, the first closed molecular container compounds, J. Am. Chem. Soc., 110, 2554 (1988)

5.Hasan A. K., Ray A. K., Nabok A. V. and Davis F., Spun film of novel calyx[4]resorcinarene derivatives for benzene vapour sensing, Sens. Actuators B, 77, 638 (2001)

6. Perret F, Lazar AN, Coleman AW (2006) Biochemistry of the para- sulfonato-calix[n]arenes. Chem Commun 42(23): 2425-2438

7. Perret F, Coleman AW (2011) Biochemistry of anionic calix[n]arenes Chem Commun (Camb) 47(26): 7303-7319

8.NCIt

9. FDA Pharma classes

10.Metzger, J. O. 1998. Solvent-Free Organic Synthesis, Angew. Chem. Int. Ed., 37:2975–2978.