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Research Article

COUMARIN AS A VERSATILE SYNTHON IN MEDICINAL CHEMISTRY

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ABSTRACT

Coumarins are used for various biological activities from ancient times, recently researchers developed novel synthetic and semisynthetic coumarin based therapeutic agents. Molecular hybridization concept using different coumarins is used in the synthesis of many of these agents. The nucleophilic and electrophilic properties of coumarins make them potential candidates for substitutions and hybridization to synthesize new drug molecules. The present review shows the coumarin as a potent scaffold for the substitution and molecular hybridisation with other heterocyclic rings.

Keywords: Coumarin, Scaffold, Synthon and Hybrids.

INTRODUCTION

Coumarins chemically Benzopyran-2-ones or Chromene-2-ones constitute a group of compounds that are widely distributed in plants[1], fungi and bacteria[2]. The name coumarin has been derived from a French word '*Coumarou*', the vernacular name of tonka beans (*Dipteryx odorata* of family Fabaceae) first isolated by Vogel in 1820[3]. These belong to the flavonoid class of plant secondary metabolites and have a broad range of biological activities, usually associated with low toxicity[4]. Coumarins are widely distributed in different parts of plants and have high concentrations in fruits (Bael), seeds (tonka beans), roots (*Ferulago campestris*) and leaves (*Murraya paniculata*)[5]. Some chemical constituents which possess coumarin skeletons are also present in plants such as *Artemisia annua*[6], *Ferula sinaica*[7], *Ammi majus*[8], *Arabidopsis thaliana*[9], *Paramignya monophylla*[10], *Kayea assamica*[11], *Mansonia gagei*[12], *Haplopappus multifolius*[13].

Some representative examples of natural coumarins are pyranocoumarin, psoralen, esculetin, scopoletin, bergapten and umbellifereone (Figure 1).

Figure 1

Coumarins of natural and synthetic origin are used as active pharmaceutical ingredients due to their outstanding therapeutic potential such as anticancer[14-16] antitubercular[17], anticoagulant [14], antimicrobial[18,19], anti-inflammatory[14,20,21], anti-HIV[22], analgesic[23], antiplatelet[24,25], antiviral [26,27], antibacterial[28], antimalarial[29] and antifilarial[30] activities.

Coumarins possess both nucleophilic and electrophilic properties so it may undergo a number of reactions which results into synthesis of new coumarin derivatives or hybrid molecules[31]. So it may be considered as a versatile synthon in organic and medicinal chemistry to synthesize new molecules.

Over the last few decades molecular hybridization become a tool in drug designing for synthesis of new molecules which are combinations of two or more pharmacophores and have ability to act on the same target on different sites or on two or more targets to give superior biological action[32]. The multifunctional attribute of these hybrid compounds makes them potential drug candidates for the treatment of multifactorial diseases such as cancer, AIDS, malaria and cardiovascular diseases.

Coumarins are important tools for molecular hybridization to get more potent hybrids with multiple biological activities, high selectivity, favorable pharmacokinetic parameters and lesser or no side effects, by conglomeration with other heterocyclics.

COUMARIN BENZIMIDAZOLE DERIVATIVES

Mentese *et al* (2015) synthesized a series of coumarins containing benzimidazole derivatives by reacting benzimidazole hydrazides and 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-

one in ethanol in absence of any catalyst[33] (Scheme **1**).

Scheme 1

Bansal *et al* (2014) synthesized two series of compounds by reacting 3 substituted coumarin with *O*-phenylenediamine and 2 substituted benzimidazole through single bond, and amide linkage respectively. Coumarin carboxylic acid was fused with *O*-phenylenediamine in the presence of polyphosphoric acid (PPA) under nitrogen. 2-aminobenzimidazole (0.01 mol) was reacted with Coumarin carboxylic acid in dried DCM and freshly distilled pyridine along with DMAP to incorporate amide linkage[34] (Scheme 2).

Scheme 2

Tsay *et al* (2013) synthesized coumarin hinged benzimidazole derivatives. 3-ethoxycarbonylcoumarins were reacted with 1,2-phenylenediamine in presence of *o*-phosphoric acid to yield coumarin benzimidazole hybrids which were further subjected to synthesize their ribofuranosides to inhibit hepatitis C virus[35] (Scheme 3).

Scheme 3

Paul *et al* (2013) reported synthesis of conjugated coumarin benzimidazole hybrids and evaluated for anticancer activity. 7-Bromo-2-oxo-2*H*-chromene-3-carboxylic acid was treated with *O*-phenylenediamine in polyphosphoric acid (PPA) to obtain two types of intermediate products which were separated through column chromatography. Further one of them was treated in two ways for synthesis of 3-(1*H*-benzo[d]imidazol-2-yl)-2*H*-chromen-2-one analogs, in first it was substituted with different primary amines at 7-position of coumarin ring in ethanol using triethylamine as base to obtain compounds A-D. In other reaction route the intermediate Compound was refluxed with primary and secondary amines using K_2CO_3 as base and $TBAHSO_4$ as catalyst in acetonitrile for 6–8 h, gave compounds E-H. In another reaction 5-dimethylamino-naphthalene-1-sulfonic acid {2-[3-(1*H*-benzimidazol-2-yl)-2-oxo-2*H*-chromen-7-ylamino]ethyl}-amide was prepared by reacting 3-(1*H*-benzimidazol-2-yl)-7-bromo-chromen-2-one in isopropyl alcohol (IPA) with 5-dimethylamino-naphthalene-1-sulfonic acid-(2-amino-ethyl)-amide[36] (Scheme 4).

Scheme 4

Hwu *et al* (2008) synthesized two series of coumarin benzimidazole conjugates. Benzimidazole derivatives were prepared from the reaction of substituted phenylenediamines with carbon disulfide and ethanolic KOH in H_2O, subsequently aqueous NH_4OH (35 %) and 3-(chloromethyl)coumarins was added to yield benzimidazole–SCH_2–coumarin derivatives[37] (Scheme 5).

Scheme 5

In other reaction symmetrical benzimidazole-2-thiones were reacted with β-d-glucose peracetate to give benzimidazole glucosidic 2-thiones which were subsequently alkylated with various 3-(chloromethyl)coumarins to generate *N*-glucosides of benzimidazole–SCH_2–coumarin conjugates[37] (Scheme 6).

Scheme 6

COUMARIN CHALCONE DERIVATIVES

El-Sherief *et al* (2017) reported synthesized new coumarin–chalcone NO hybrids of potential biological activity. 2-Bromo-N-{4-[3-arylacryloyl]-phenyl}acetamides were synthesized and reacted with 7-Hydroxy-4-methyl coumarin to obtain 2-(4-Methyl-2-oxo-2*H*chromen-7-yloxy)-N-(4-((E)-3-phenylacryloyl)phenyl) acetamides which were then treated with hydroxylamine hydrochloride to give final products (Scheme7), 2-(4-methyl-2-oxo-2Hchromen-7-yloxy)-N-(4-(1-(hydroxyimino)-3-(phenyl)-allyl)phenyl)acetamides[38] (Scheme 7).

Scheme 7

Kurt *et al* (2017) reported synthesis of coumarin-chalcone derivatives containing urea moiety as potential anticancer agents. 3-Acetyl coumarin was synthesized from salicylaledyde which was further reacted with p-nitrobenzaldehyde to give corresponding chalcone. Nitro group was reduced to NH_2 in next step and the compound so obtained was further reacted with R-phenylisocyanate to yield final products[39] (Scheme 8).

Scheme 8

Pingaew *et al* (2014) synthesized chalcone coumarin hybrids and evaluated for anticancer and antimalarial activity. Chalcones were first prepared by base-catalyzed Claisen Schmidt condensation of aldehydes and amino acetophenones which were subjected for azotization reaction in presence of sodium nitrite and sodium azide in a mixture of glacial acetic acid and concentrated hydrochloric acid to give the corresponding azidochalcones. These azidochalcones were subjected for cycloaddition with alkynes of 4-hydroxycoumarin or 7-hydroxycoumarin to get the novel desired hybrid molecules[40] (Scheme 9).

Scheme 9

COUMARIN IMIDAZOLE DERIVATIVES

Hu *et al* (2018) synthesized a number of coumarin derivatives containing imidazole skeleton as potential antibacterial agents. Two derivatives a and b showed potent and broad

spectrum antimicrobial activity while three c, d and e show eminent antimicrobial efficacy toward *S. aureus*, *S. agalactiae*, and *F. cloumnar.* Dibromoalkanes were reacted with 7- Hydroxy coumarin to obtain intermediates which were further treated to get coumarin imidazole derivatives[41] (Scheme 10).

Scheme 10

Rajanarendar *et al* (2014) reported synthesis of tri heterocyclic derivatives of coumarin, imidazole and isoxazole. 4-amino-3-methyl-5-styrylisoxazoles was reacted with 3-(2-bromoacetyl) coumarin in absolute ethanol to yield 3-[2-(3-methyl-5-styryl-4-ylamino)acetyl]chromen-2-ones which were subsequently cyclized by treating with KSCN to give 3-[1-(3-methyl-5-styryl-isoxazol-4yl-)-2-mercapto-1*H*-imidazol-4yl]-1-benzopyran-2*H*-ones (Scheme 11). These were further treated to get final derivatives[42].

Scheme 11

Liu *et al* (2016) synthesized coumarin imidazole hybrids and evaluated for anthelmintic activity against Dactylogyrus intermedius in goldfish. 7-Hydroxycoumarin was reacted with alkyl dibromide and further bromoalkane and substituted imidazole was added to this compound to get four bromide and twenty imidazole derivatives respectively. 7-(4-(1*H*-imidazol-1-yl)butoxy)-2*H*-chromen-2-one (Compound A) (Figure 2.) show best anti anthelmintic activity with EC_{50} value of 0.85 mg/L[43].

Figure 2

COUMARIN INDOLE DERIVATIVES

Gu *et al* (2019) synthesized indolo[2,3-*c*]coumarins and indolo[2,3-*c*]quinolinones via microwave-assisted base-free intramolecular cross dehydrogenative coupling (CDC). Aniline substituted coumarins and quinolinones were coupled utilizing $Pd(OAc)_2$ as the catalyst, AgOAc or air as the oxidant, with or without CsOAc as the base and PivOH or AcOH as the solvent[44] (Scheme 12).

Scheme 12

Aksungar *et al* (2018) used Knoevenagel condensation, to synthesize coumarin-indole based push pull dyes. 2-(1-(7-(diethylamino)-2-oxo-2*H*-chromen-3-yl)ethylidene)malononitrile was synthesized and was reacted with indole-3-carbaldehyde, or 1-methyl-1*H*-indole-3-carbaldehyde in ethanol as solvent and piperidine as catalyst to get two coumarin-indole conjugate push–pull chromophores[45] (Scheme 13).

Scheme 13

Kamath *et al* (2015) synthesized three series of indole-coumarin hybrids, 3-(1-benzyl-1*H*-indol-2-yl)-2*H*-chromen-2-ones, 2-(2-oxo-2*H*-chromen-3-yl)-1*H*-indole -3-carbaldehydes and 2-(2-oxo-2*H*-chromen-3-yl)-1*H*-indole-3 carboxylic acids from Phenyl hydrazine and substituted 3-acetyl-chromen-2-ones[46] (Scheme 14).

Scheme 14

Sashidhara *et al* (2010) synthesized two series of coumarin bisindole derivatives. The Duff reaction on naphthalen-1-ol gave intermediate compound, which was engaged in a Knoevenagel type reaction with appropriate active methylene compounds, resulting in the formation of coumarinic compounds. Subsequently, an efficient electrophilic substitution of different indoles with these coumarin aldehydes derivatives using acetonitrile in presence of iodine yield coumarin bisindole hybrids. Similarly, another series of coumarin bisindole hybrids were prepared starting from 2-sec-butylphenol which was subjected to same series of steps resulting in another set of coumarin bisindole hybrids[47] (Scheme 15).

Scheme 15

COUMARIN OXAZOLE/OXADIAZOLE DERIVATIVES

Dhawan *et al* (2018) synthesized coumarin-tagged 1,3,4-oxadiazole conjugates and evaluated against MDA-MB-231 and MCF-7 human breast cancer cells. Coumarin hydrazides were prepared from previously synthesized ethyl 2-((4,5-dimethyl-2-oxo-2H-chromen-7-yl)oxy)acetate and cyclized by treating with CS_2 and KOH in ethanol to synthesize coumarin oxadiazole derivatives. These were further treated to yield final derivatives[48] (Scheme 16).

Scheme 16

Bhinder and colleague (2015) synthesized 3-(5-mercapto-1, 3, 4-oxadiazol-2-yl)-2*H*-chromen-2-one derivatives and evaluated for anticancer activity. These were synthesized from 2-oxo-2*H*-chromene-3-carbohydrazide in presence of CS_2/KOH and were further refluxed in presence of base and alkalyting agents to yield different derivatives[49] (Scheme 17).

Scheme 17

Krishna *et al* (2015) synthesized 4-[(3-aryl-1,2,4-oxadiazol-5-yl)methoxy]-coumarins, 6-[(3-aryl-1,2,4-oxadiazol-5-yl)methoxy]-4-methylcoumarins and 7-[(3-aryl-1,2,4-oxadiazol-5-yl) methoxy]-4-phenylcoumarins in high yields by one-pot condensation reaction of esters with amidoximes[50] (Scheme 18).

Scheme 18

Bhat *et al* (2013) reported synthesis of Schiff bases of coumarin incorporated 1,3,4-oxadiazole derivatives and evaluated for antimicrobial activity. 3-{5-[(E)-(substituted benzylidene)

amino]-1,3,4-oxadiazol-2-yl}-2H-chromen-2-ones were synthesized by treating substituted benzaldehydes with 3-(5-amino-1,3,4-oxadiazole-2-yl)-2*H*-chromen-2-one to form schiff bases[51] (Scheme 19).

Scheme 19

Patel *et al* (2013) synthesized coumarin-based 1,3,4-oxadiazol-2ylthio-N-phenyl/benzothiazolyl acetamides from coumarin-3-carboxylic acid ethyl ester obtained through Knoevenagel and Pinner reaction[52] (Scheme 20).

Scheme 20

Patel *et al* (2012) synthesized Quinolone and Coumarin Based 1,3,4-Thiadiazolyl and 1,3,4-Oxadiazolyl *N*-Mannich bases. The hydrazides of 4-hydroxy quinolone and coumarins were refluxed in carbon disulfide in ethanolic potassium hydroxide to obtain the corresponding hydrazine carbodithioate salts which were further treated in two ways with sulfuric acid or hydrochloric acid at cooled temperature to give the corresponding 1,3,4-thiadiazole and 1,3,4-oxadiazole intermediates, respectively, these were then treated with piperazine bases in the presence of formalin in methanol to yield the final *N*-Mannich products[53](Scheme 21).

Scheme 21

Laxami *et al* (2013) reported synthesis of a series of 5-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4a–f) and dihydro-5-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione derivatives by the condensation of 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde with barbituric acid and thiobarbituric acid in acetic acid under microwave irradiation method[54] (Scheme 22).

Scheme 22

COUMARIN PIPERAZINE DERIVATIVES

Zhang *et al* (2018) reported synthesis of coumarin piperazine hybrids and evaluated as acetylcholinesterase inhibitors. To 2-Oxo-2*H*-chromene-3-carboxylic acid which was prepared from 2-hydroxybenaldehyde and Meldrum's acid, was added 1-Boc-piperazine in dry dichloromethane in presence of EDCI, HOBT and N,N-diisopropylethylamine, which give 4-(2-oxo-2*H*-chromene-3-carbonyl)piperazine-1-carboxylate. Which was further treated with substituted bromides (RCH_2Br) to get final compounds[55] (Scheme 23).

Scheme 23

Koparde *et al* (2018) synthesized coumarin piperazine derivatives by reacting 1-(4-(4-hydroxyphenyl)piperazin-1-yl)ethanone with substituted 4-bromomethyl coumarins in DMF under catalytic amount of K_2CO_3[56] (Scheme 24).

Scheme 24

Govindhan *et al* (2015) reported another method for synthesis of coumarin piperazine derivatives. 4-hydroxycoumarin was treated with ethyl bromoacetate to synthesise ethyl 2-(2-oxo-2H-chromen-4-yloxy)acetate, which was further reacted with solution of lithium hydroxide in THF to get 2-(2-Oxo-2H-chromen-4-yloxy)acetic acid. To this acid was added piperazine in DMF in presence of EDCI and HOBt to get 4-(2-(piprazine-1-yl)ethoxy)-2H-chromen-2-one. Which was further treated with acid chlorides(R) or trifluoroacetic anhydride(R) or corresponding sulphonyl chloride(R) or io doacetamide(R) in DMF in presence of triethylamine to get desired products[57] (Scheme 25).

Scheme 25

Sweta and coworker (2014) 2,4-Dichloro-6-(4-methoxyphenyl)-1,3,5-triazine was reacted with 4-hydroxy coumarin to get 4-((4-Chloro-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one, which was subsequently reacted with N-substituted piperazine derivatives to get 4-((4-(4-Methoxyphenyl)-6-(4-substituted piperazin-1-yl)-1,3,5-triazin-2-yl)oxy)-2*H*chromen-2-one derivatives[58] (Scheme 26).

Scheme 26

Wang *et al* (2014) synthesized two series of coumarin piperazine derivatives. In one reaction 4-hydroxy coumarin was reacted with epoxy chloropropane and the product was treated with substituted piperazine to get coumarin piperazine derivatives. In another reaction 2-bromo-1-(4-methylpiperazin-1-yl)ethanone was synthesised and was reacted with 4-hydroxy coumarin to get another series of coumarin piperazine derivaives[59] (Scheme 27).

Scheme 27

COUMARIN PYRAZOLE DERIVATIVES

Liu *et al* (2018) synthesized some coumarin-pyrazole carboxamide derivatives as potential topoisomerase II inhibitors. Coumarin-3-carboxylic acid was (synthesized from 2-hydroxybenzaldehydes and 2,2-dimethyl-1,3-dioxane-4,6-dione) reacted with ethyl 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylate derivatives (synthesized from ethyl (E)-2-cyano-3-ethoxyacrylate and phenyl hydrazine hydrochloride) to get 2-oxo-N-(1-phenyl-1H-pyrazol-5-yl)-2H-chromene-3-carboxamide derivatives[60] (Scheme 28).

Scheme 28

Zhu *et al* (2017) synthesized pyrazole coumarin derivatives as dual inhibitors of COX-2 and 5-LOX by hybridization of pyrazoles with substituted coumarins. A series of pyrazole sulfonamide carboxylic acids was synthesized and reacted with substituted coumarins (3-carboxy coumarin, 4-hydroxycoumarin and 7-hydroxycoumarin) with the incorporation of different linkers to get different derivatives[61] (Scheme 29).

Scheme 29

Angelova *et al* (2017) synthesized 2-aroyl-benzopyrano[4,3-c]pyrazol-4(1H)-one derivatives, The reaction of 4-chlorocoumarin-3-carbaldehyde with corresponding hydrazides in EtOH:CH_2Cl_2 (1:3) resulted in N-2-substituted chromeno[4,3-c]pyrazol-4-one analogues[62] (Scheme 30).

Scheme 30

Vaarla *et al* synthesized Coumarin substituted thiazolyl-3-aryl-pyrazole-4-carbaldehydes from 3-(2-bromoacetyl)-2*H*-chromen-2-one, thiosemicarbazide and acetophenone in presence of dimethylformamide via one pot reaction and further applying Vilsmeyer-Hack formylation reaction conditions[63] (Scheme 31).

Scheme 31

Thakor *et al* (2014) synthesized pyrazole substituted coumarin derivatives by the reacting 4-hydroxy coumarin**,** 3-(4-hydroxy phenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes and malanonitrile in presence of piperidine and ethanol as solvent[64] (Scheme 32).

Scheme 32

In another series 7-Acetyloxy 4- methyl coumarin was used instead of 4-Hydroxy coumarin to get another series of pyrazole coumarin derivatives[64] (Scheme 33).

Scheme 33

Kenchappa *et al* (2014) synthesized coumarin derivatives containing pyrazole and indenone rings. 5,6-Dimethoxy-2,3-dihydro-1*H*-inden-1-one and 3-(6-substituted-2-oxo-2*H*-chromen-3-yl)-1-(4-substituted)-1*H*-pyrazole-4-carbaldehyde (synthesized from reacting 3-acetyl coumarin and phenyl hydrazines) was reacted to get 3-(4-((Z)-(5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)-1-4-substituted-phenyl-1*H*-pyrazol-3-yl)-6-substituted2*H*-chromen-2-one derivatives[65] (Scheme 34).

Scheme 34

COUMARIN PYRIDINE DERIVATIVES

Vafadarnejad *et al* (2018) synthesized coumarin-pyridinium hybrids and evaluated for acetyl cholinesterase (AChE) and butyryl cholinesterase (BChE) inhibitor activity. Pyridin-3-yl methanamine or pyridin-4-yl methanamine were fused with coumarin-3-carboxylic acid in presence of EDCI and HOBt in dry acetonitrile to give intermediate compounds which were further reacted with appropriate benzyl halides in dry acetonitrile[66] (Scheme 35).

Scheme 35

Naik *et al* (2018) synthesized coumarin linked with pyrimidine derivatives *via* microwave irradiation. 3-acetyl coumarin was synthesized from salicylic aldehyde and acetyl acetic ester in presence of ethanol and few drops of piperidne. Coumarin chalcones were synthesized from Claisen-Schmidt condensation of 3-acetyl coumarin and different substituted benzaldehydes which were irradiated in microwave reactor with isonicotinamidine hydrochloride in dry DMF under 215 W power at 150 ^oC for about 15-20 min[67] (Scheme 36).

Scheme 36

Jiabin Li and coworkers (2017) reported synthesis of 2-phenylpyrimidine coumarin derivatives as anticancer agents. Ethyl cyanoacetate, salicylic aldehyde, 3-hydroxybenzaldehyde, and ammonium acetate were reacted to get intermediates which were further reacted with the substituted sulfonyl chloride to obtain 3-sulfonate-substituted 2-phenyl-benzopyrano pyrimidine derivatives[68] (Scheme 37).

Scheme 37

Elshemy and Zaki (2017) reported another series of coumarin pyridine derivatives. 3-acetyl coumarin was reacted with equimolar of dimethylformamide-dimethylacetal (DMF-DMA) in refluxing toluene to get the corresponding enaminone, which upon condensation with acetyl acetone or ethyl acetoacetate in glacial acetic acid in the presence of ammonium acetate give pyridine hybrids[69] (Scheme 38).

Scheme 38

In another reaction picolinonitrile derivatives were prepared by treating chalcone derivatives with malononitrile using ammonium acetate in glacial acetic acid[69] (Scheme 39).

Scheme 39

Brahmbhatt *et al* (2012) synthesized coumarin and indenopyridine hybrids 3-coumarinyl methyl pyridinium salts were treated with appropriate 2-arylidene-1-indanones in the presence of ammonium acetate in glacial acetic to obtain 3-(4-aryl-5*H*-indeno[1,2-b] pyridin-2-yl) coumarins via Krohnke's reaction mechanism[70] (Scheme 40).

Scheme 40

COUMARIN THIAZOLE DERIVATIVES

Ayati *et al* (2018) synthesized coumarins bearing 2,4 diaminothiazole-5-carbonyl derivatives and evaluated for cytotoxic effects against tested cell lines MCF-7, HepG2 and SW480. 3-(bromoacetyl)coumarins were reacted with intermediates obtained by reacting dimethyl N-cyanodithioimidocarbonate with appropriate cyclic amine and sodium sulfide to produce a series of final derivatives[71] (Scheme 41).

Scheme 41

In another reaction between phenylisothiocyanates and cyanamide in the presence of sodium methoxide gives another intermediates which were then treated with 3-(bromoacetyl) coumarin to give 3-(4-amino-2-(arylamino)thiazole-5-carbonyl)-2*H*-chromen-2-ones[71] (Scheme 42).

Scheme 42

Kavitha *et al* (2018) synthesized two series of coumarin thiazole linked with 3-phenylacrylonitriles and 3-heterylacrylonitriles. by treating equimolar amounts of 3-(2-bromoacetyl)-2H-chromen-2-one with 2-cyanothioacetamide and various aryl/heteryl aldehydes. All these synthesized compounds were further screened for the anti-hepatocarcinoma activity with the support of molecular docking studies[72] (Scheme 43).

Scheme 43

Mangasuli *et al* (2018**)** reported a series of C-N bridged coumarin-thiazolidine-2,4-dione derivatives, which were further evaluated for *in vitro* anti microbial and anti inflammatory activities. (*Z*)-5-(4-substituted-benzylidene)-3-(substituted-2-oxo-2*H*-chromen-4-yl) methyl] thiazolidine-2,4-dione derivatives were synthesized by the Condensation of 4-bromomethyl coumarin with (*E*)-5-benzylidenethiazolidine-2,4-diones[73] (Scheme 44).

Scheme 44

Ibrar *et al* (2016) synthesized a series of coumarin thiazole hybrids and screened for their inhibitory activity against aldose reductase (ALR2). Coumarinyl hydrazide was reacted with carbon disulfide in the presence of ethanolic solution of KOH under reflux to get corresponding 3-(5-thioxo-4,5-dihydro-1,3,4-oxa diazol-2-yl)-2H-chromen-2-one which were treated with paraformaldehyde and different amines to get coumarinyl oxadiazole-2(3H)-thione hybrids[74] (Scheme 45).

Scheme 45

Osman *et al* (2018) and coworkers synthesized coumarin thiazole hybrids through Hantzsch cyclisation of 3-(2-bromoacetyl)-2*H*-chrome-2-ones with different *N*-substituted thiourea or *N,N*-di-substituted thiourea[75] (Scheme 46).

Scheme 46

OTHER COUMARIN DERIVATIVES

Mangasuli *et al* (2017) synthesized coumarin theophylline hybrids and evaluated for antitubercular and antimicrobial activity. 4-bromomethyl coumarins (synthesized by Pechman cyclisation of phenols with 4-bromoethylacetoacetate using sulphuric acid) were condensed with theophylline to get 1,3-dimethyl-9-[(substituted-2-oxo-2*H*-chromen-4-yl)methyl)-1*H*-purine-2-dione derivatives in anhydrous K_2CO_3 using acetone as solvent[76] (Scheme 47).

Scheme 47

Najafi *et al* (2019) recently reported the synthesis of novel tacrine-coumarin hybrids linked to 1,2,3-triazole. Desired propargylated acridine derivatives and azide derivatives were prepared and were subjected to click reaction in H_2O/*t*-BuOH (1:1) in the presence of Et_3N along with a catalytic amount of CuI at room temperature for 12–24 h to get final hybrids[77] (Scheme 48).

Scheme 48

CONCLUSION

The present review gives an outlook on the coumarin scaffold, as it possesses both electrophilic and nucleophilic nature so it may undergo a number of naming and substitution reactions. The coumarin scaffold may be considered as a potential candidate for molecular hybridization as a number of hybrids have been synthesized in recent years and were evaluated for a wide range of biological activities.

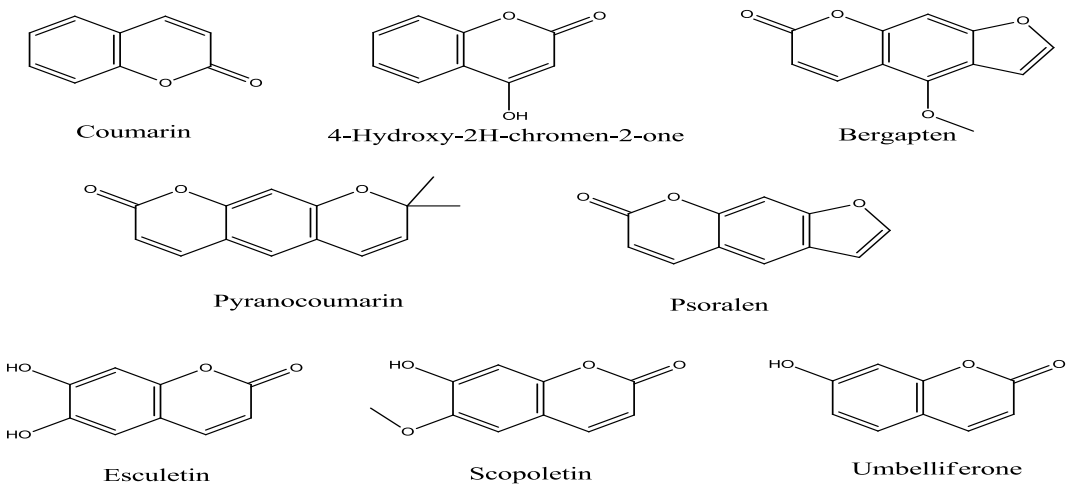


Fig. 1: Examples of natural coumarins

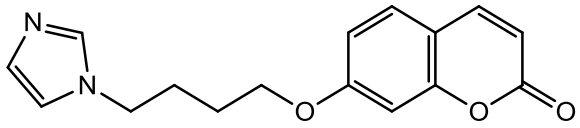
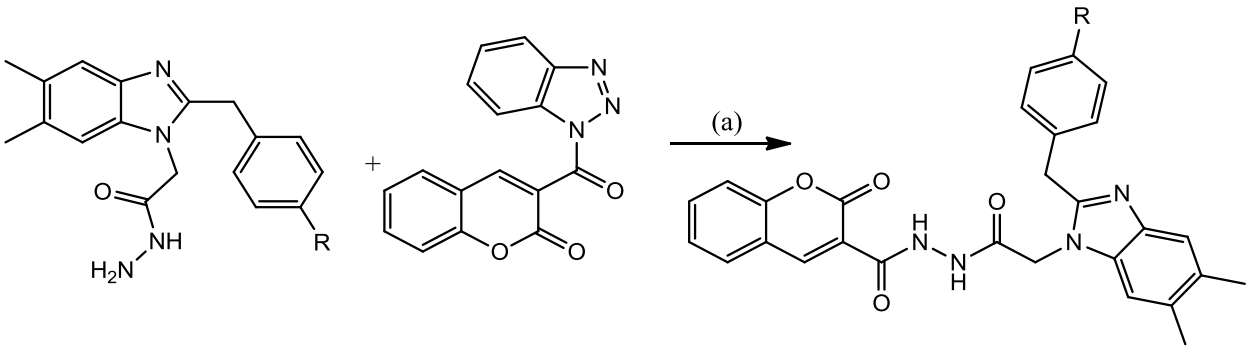
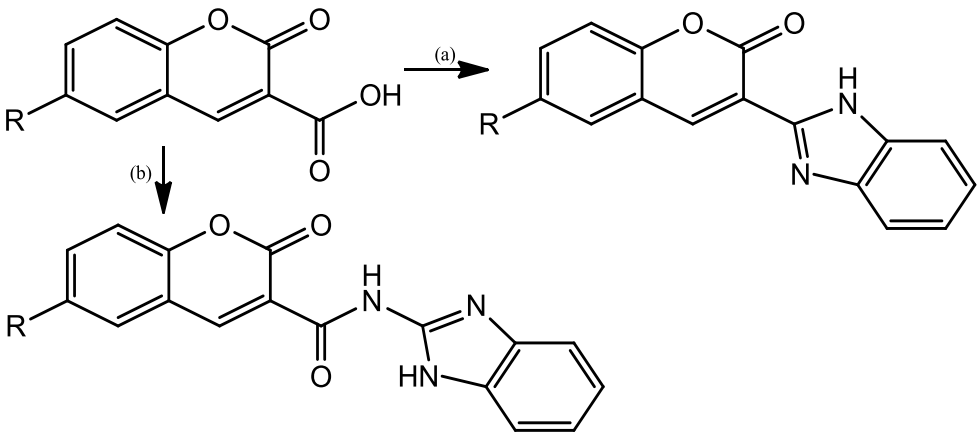


Fig. 2: 7-(4-(1*H*-imidazol-1-yl)butoxy)-2*H*-chromen-2-one (Compound A)



Reaction conditions: (a) Ethanol, reflux, 6 h R = CH_3, F, Cl, OCH_3, NO_2, Br

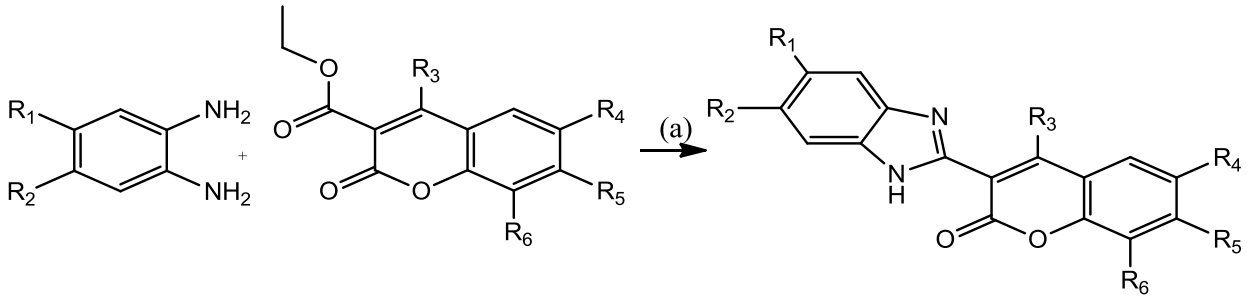
Scheme. 1:



Reaction conditions: (a) O-phenylenediamine, PPA, reflux, 115 °C
(b) DMAP, DCC, 2-amino benzimidazole

R = H, OCH_3, Br, Cl, NO_2

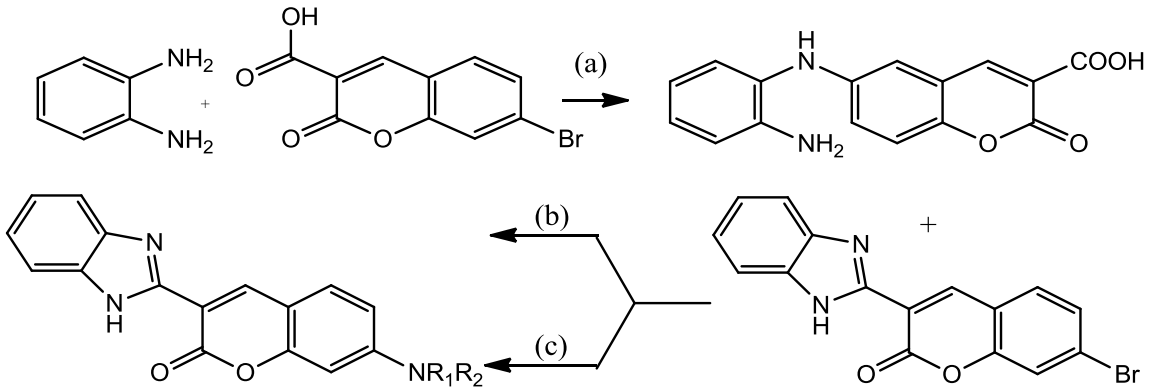
Scheme. 2:



Reaction conditions: (a) 85% H_3PO_4, 165 °C

R_1	R_2	R_3	R_4	R_5	R_6
H	H	H	H	H	H
Me	Me	Me	Br	I	OMe
F			NO_2	OAc	
COOH					

Scheme. 3:

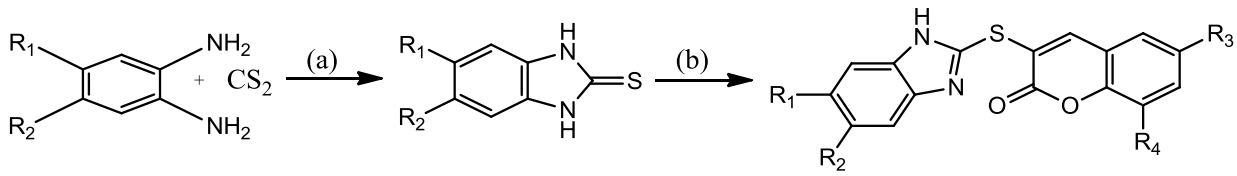


Reagents and conditions: (a) PPA (b) Ethanol, Et_3N, NHR_1R_2, (c) K_2CO_3, ACN, $TBAHSO_4$, NHR_1R_2

Compound	A	B	C	D	E
NR_1R_2	Ethylenediamine	Ethanolamine	n-Butylamine	Cyclohexylamine	4-Fluoroaniline

Compound	F	G	H
NR_1R_2	Morpholine	Methylpiperazine	2-Amino ethylmorpholine

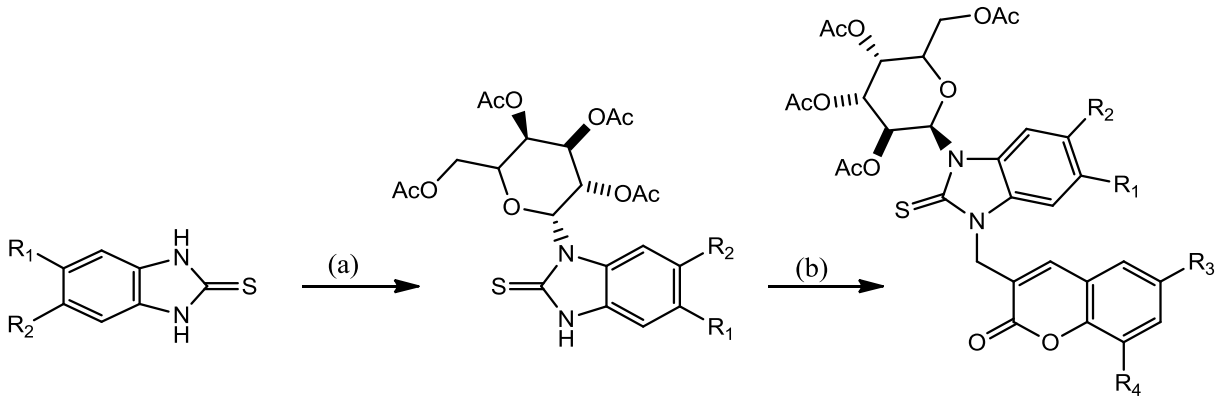
Scheme. 4:



Reagents and conditions: (a) KOH, Ethanol, H_2O (b) NH_4OH, CH_3CN, H_2O, substituted 3-(chloromethyl) coumarins

Compound	A	B	C	D	E	F	G	H	I	J	K
R_1	H	F	COPh	Me	Cl	H	H	F	F	Cl	Cl
R_2	H	H	H	Me	Cl	H	H	H	H	Cl	Cl
R_3	H	H	H	H	H	H	Br	H	Br	H	Br
R_4	H	H	H	H	H	OMe	H	OMe	H	OMe	H

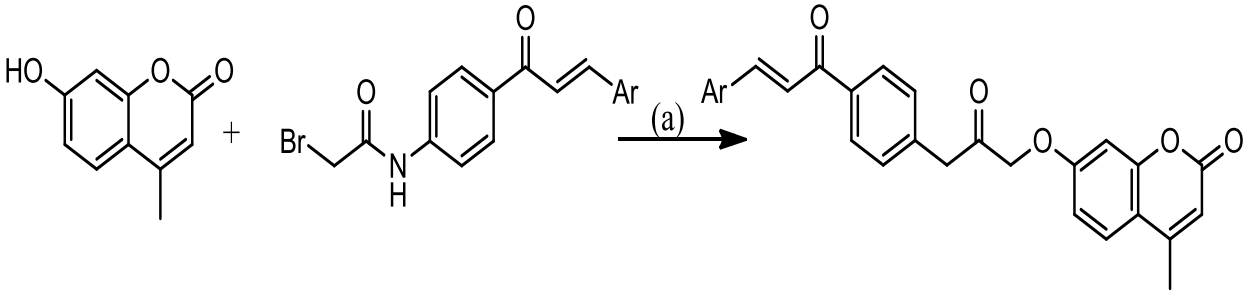
Scheme. 5:



Reagents and Conditions: (a) N,O-bistrimethylsilylacetamide, Me_3SiOTf, CH_3CN. peracetylpyranose, 80 °C (b) 35% NH_4OH, CH_3CN, H_2O

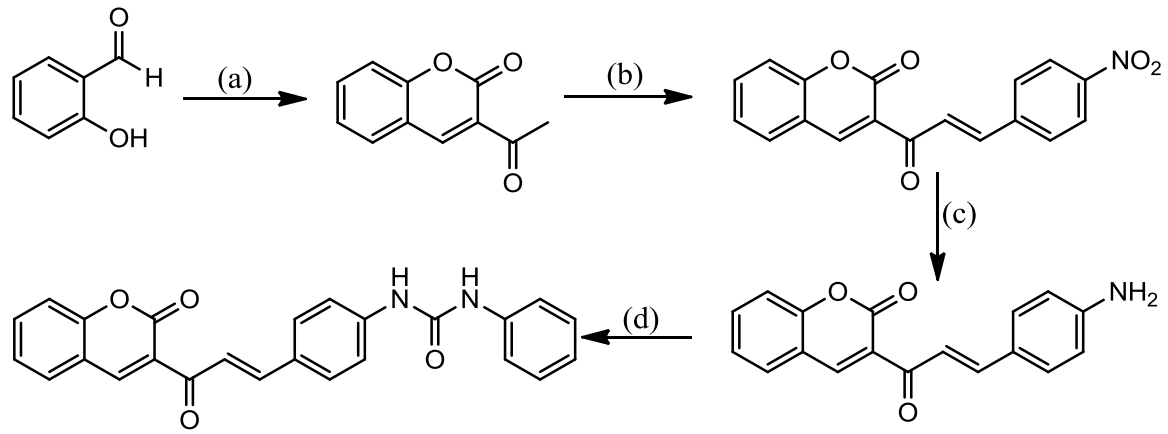
Compound	A	B	C	D	E
R_1	H	Cl	H	Cl	Cl
R_2	H	Cl	H	Cl	Cl
R_3	H	H	Br	Br	H
R_4	H	H	H	H	OMe

Scheme. 6:



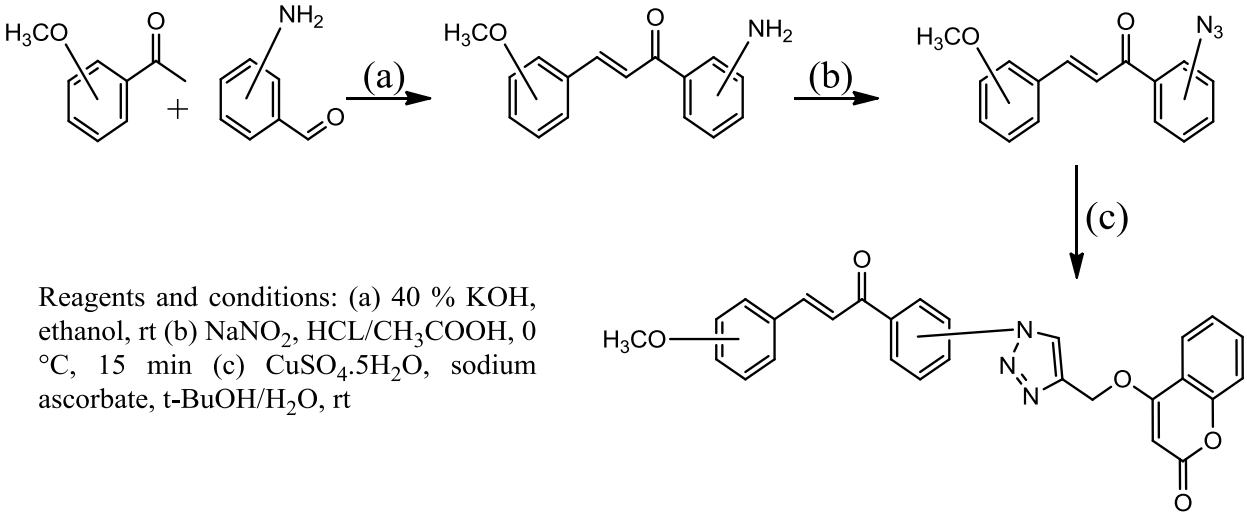
Reagents and conditions: (a) K_2CO_3, DMF, rt, stirring, 6-48 h (b) Pyridine, reflux, 3h

Scheme. 7:



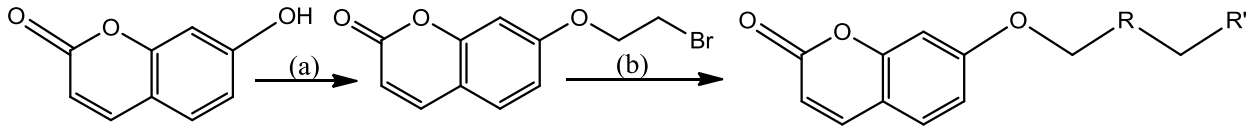
Reagents and conditions: (a) Ethylacetoacetate, piperidin, rt (b) p-nitrobenzaldehyde, piperidin, ethanol, 80 °C, 6 h (c) $SnCl_{2.2}H_2O$, ethanol, 80 °C, 2 h (d) R-phenylisocyanate, Et_3N, THF, 70 °C, overnight

Scheme. 8:

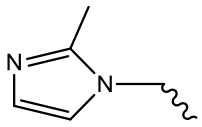
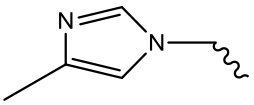
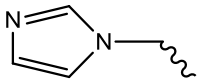
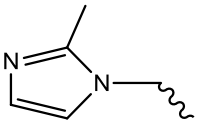
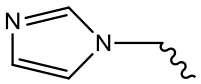


Reagents and conditions: (a) 40 % KOH, ethanol, rt (b) $NaNO_2$, HCL/CH_3COOH, 0 °C, 15 min (c) $CuSO_4.5H_2O$, sodium ascorbate, t-$BuOH/H_2O$, rt

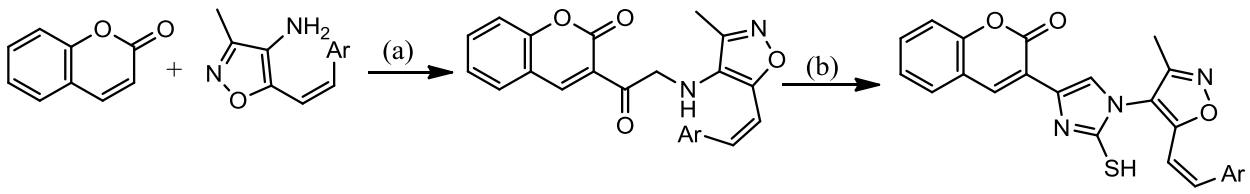
Scheme. 9:



Reagents and conditions: (a) Dibromoalkanes, triethylamine, anhydrous acetone, reflux
(b) Amines and anhydrous potassium carbonate, acetonitrile, rt

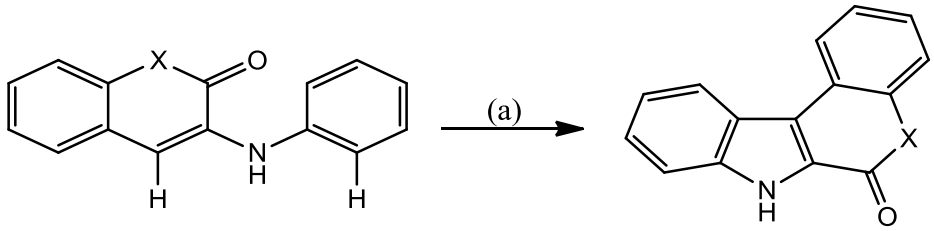
Compound	R	R'
A	$-C_4H_8-$	
B	$-C_4H_8-$	
C	$-C_6H_{12}-$	
D	$-C_6H_{12}-$	
E	$-C_6H_{12}-$	

Scheme. 10:



Reagents and conditions: (a) Ethanol (b) KSCN, acetic acid

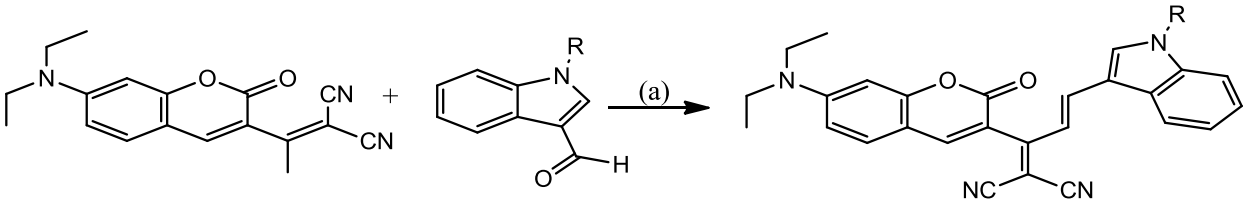
Scheme. 11:



Reagents and conditions: (a) CDC, $Pd(OAc_2)$, $Cu(OAc_2)$, PivOH, AcOH, MW, 140 °C

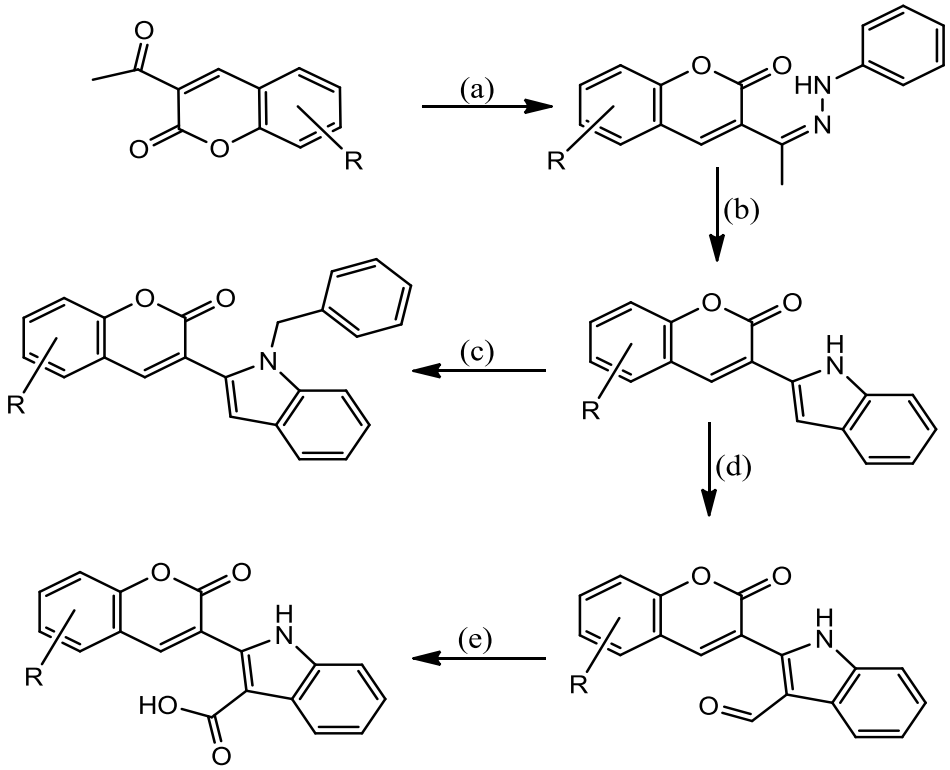
X = O or NH

Scheme. 12:



Reagents and conditions: (a) Ethanol, piperidine R = H or CH_3

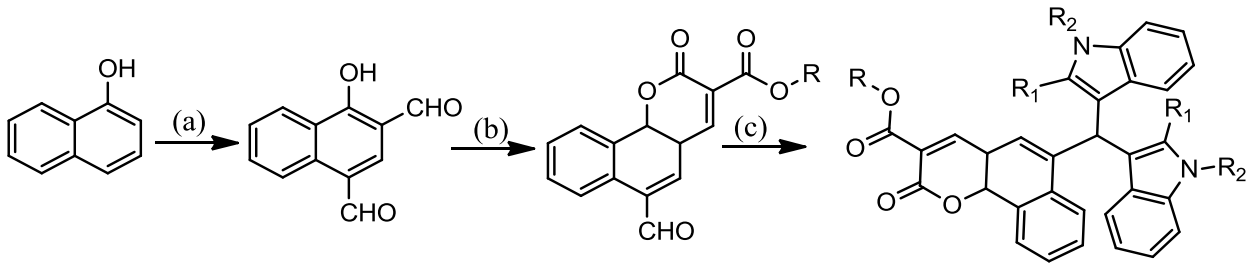
Scheme. 13:



Reagents and conditions: (a) CH_3COOH, C_2H_5, $C_6H_5NHNH_2$ (b) CH_3SO_3H, P_2O_5, (c) K_2CO_3, DMF, $C_6H_5CH_2Cl$ (d) DMF, $POCl_3$ (e) $KMnO_4$, DMF, NaOH

R = H, Cl, Br, OH

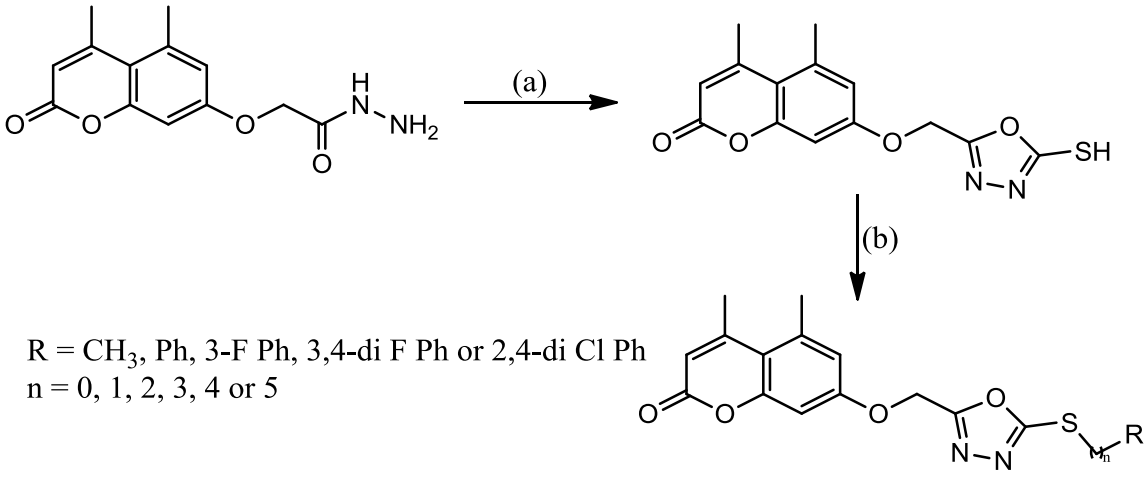
Scheme. 14:



Reagents and conditions: (a) (1) HMTA, TFA, 120 °C, 3 h (2) H_2SO_4, 90-100 °C, 2 h (b) $CH_2(COOR)_2$, ROH, piperidine, reflux, 30 min (c) Indoles, I_2, CH_3CN, 30 min

Compound	R	R_1	R_2	Compound	R	R_1	R_2
A	CH_3	H	H	E	C_2H_5	H	H
B	CH_3	H	CH_3	F	C_2H_5	H	CH_3
C	CH_3	CH_3	H	G	C_2H_5	CH_3	H
D	CH_3	CH_3	CH_3	H	C_2H_5	CH_3	CH_3

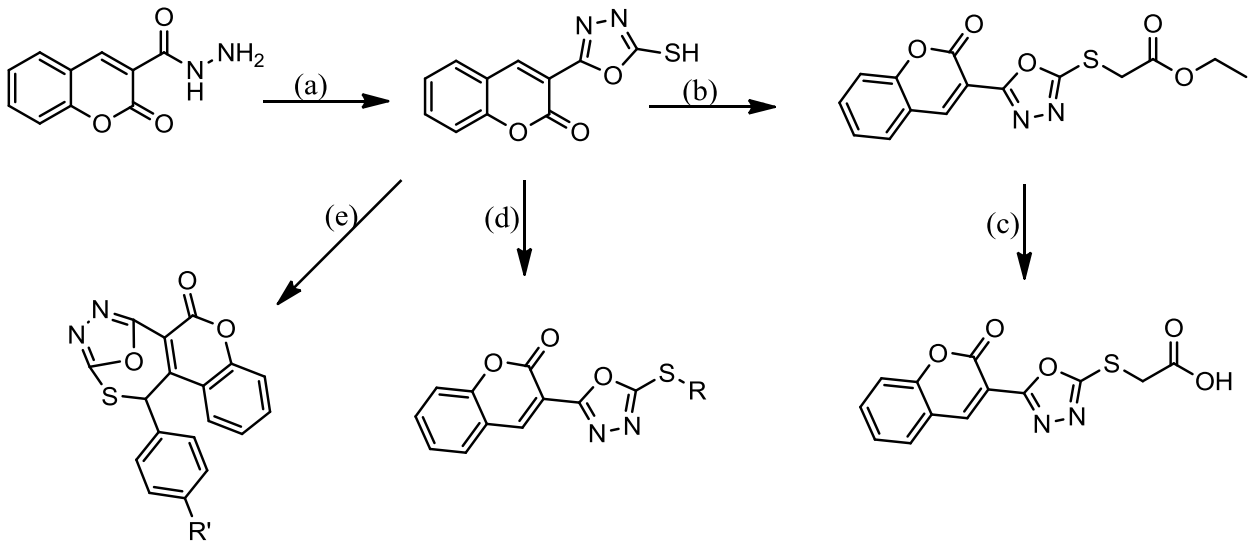
Scheme. 15:



R = CH_3, Ph, 3-F Ph, 3,4-di F Ph or 2,4-di Cl Ph
n = 0, 1, 2, 3, 4 or 5

Reagents and conditions: CS_2, KOH, ethanol, 80-85 °C, 16 h (b) K_2CO_3, rt, 2 h

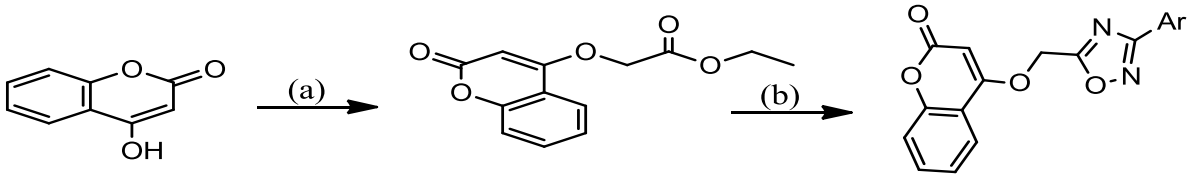
Scheme. 16:



Reagents and conditions: (a) CS_2, KOH, ethanol, refluxed (b) ethyl bromoacetate, anhyd. K_2CO_3, dry acetone, refluxed, 16 h (c) NaOH in water, ethanol, stirring, 2 h (d) alkyl halides, ethanol, 10% NaOH solution, reflux, 6 h (e) 4-substituted phenacyl halides, base, solvent, reflux

R = CH_3, C_2H_5, C_3H_7, C_4H_9 R' = Br, Cl, F

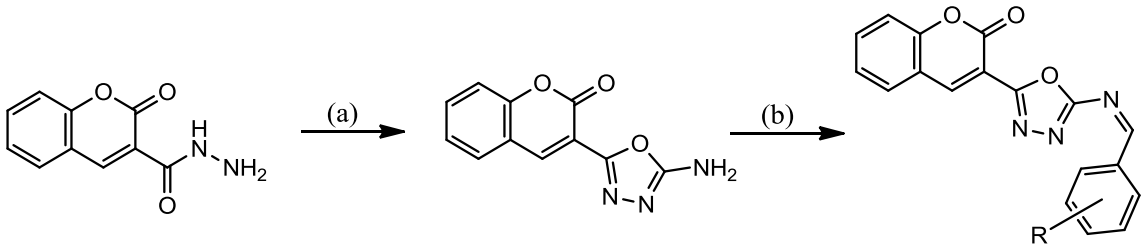
Scheme. 17:



Reagents and conditions: (a) Ethyl bromoacetate, K_2CO_3, DMF (b) Amidoximes, K_2CO_3, toluene, reflux, 24-36 h

Ar = C_6H_5, OHC_6H_4, $OCH_3C_6H_4$, C_5H_4N

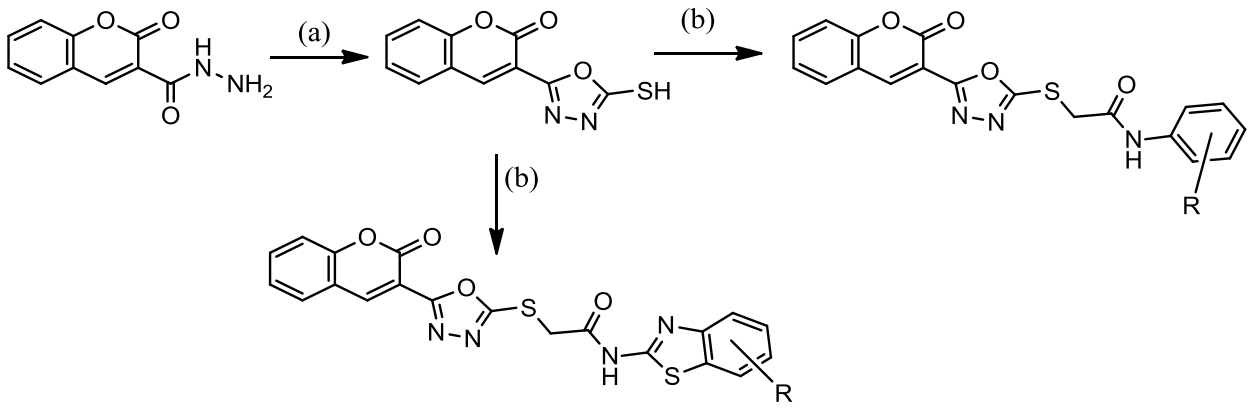
Scheme. 18:



Reagents and conditions: (a) CNBr, C_2H_5OH, 55-60 °C, 90 min (b) glacial acetic acid, 1,4-dioxan, substituted benzaldehydes, reflux, 8 h

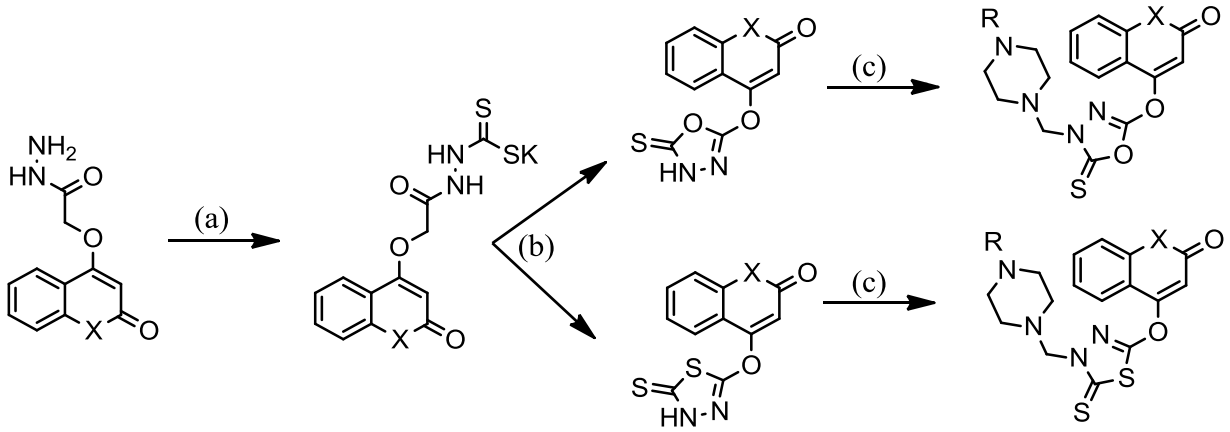
R = 3-NO_2, 3,4-$(OCH_3)_2$, 4-OH, 2-OH, 2-NO_2, 3-OH, 4-$N(CH_3)_2$, 4-F, OCH_3, 2-Cl, 3-Cl, 4-Cl, H, 4-NO_2, 3-F, 2-F, 2-OCH_3, 3-OCH_3

Scheme. 19:



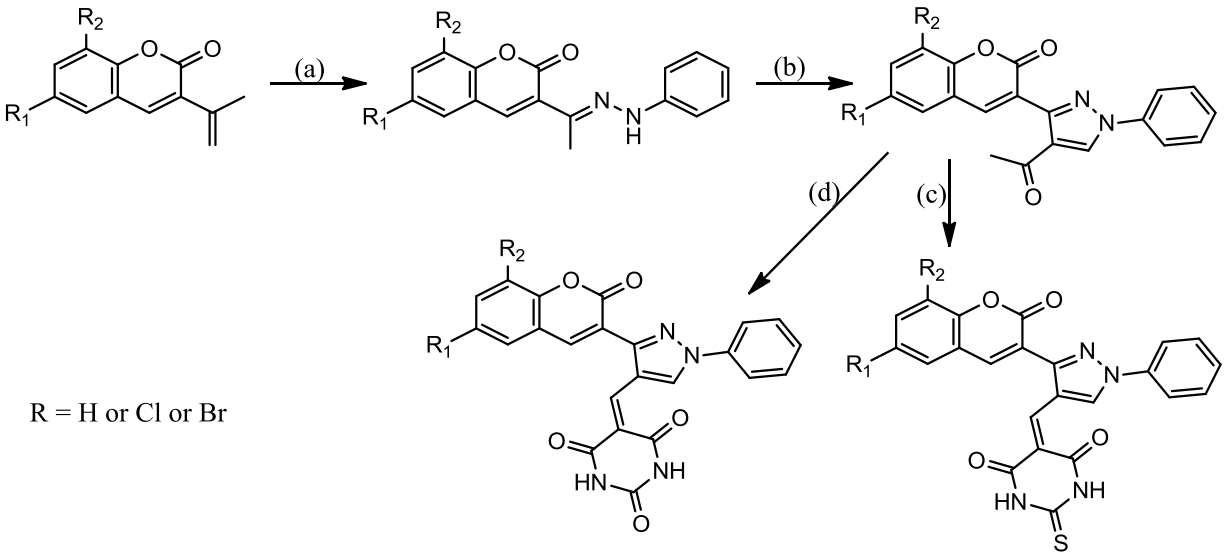
Reagents and conditions: (a) CS_2/KOH, reflux, ethanol (b) Acetone, reflux
R = H, Cl, Br, F, I, NO_2, CN, CH_3, OCH_3, OCH_2CH_3, $NHCOCH_3$

Scheme. 20:



Reagents and conditions: (a) CS_2/KOH, ethanol, reflux; (b) H_2SO_4/HCl, 0-5 °C (c) HCHO, piperazines, ethanol, reflux

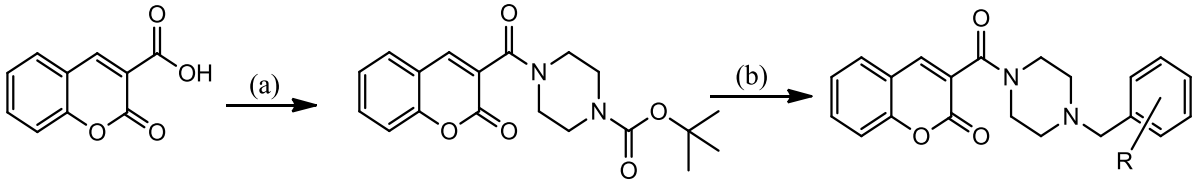
Scheme. 21:



R = H or Cl or Br

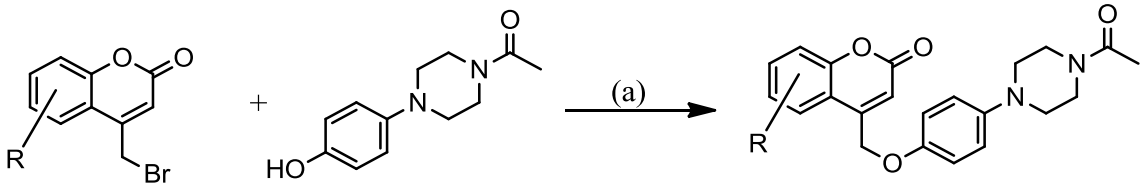
Reagents and conditions: (a) Ph-$NHNH_2$, Acetic acid (b) DMF, $POCl_3$ (c) Thiobarbituric acid, Acetic acid (d) Barbituric acid, Acetic acid

Scheme. 22:



Reagents and conditions: (a) 1-Boc-piperazine, EDCI, HOBT, DCM, DIEPA, 16 h (b) (1) CF_3COOH, DCM, 0 °C (2) RCH_2Br, Et_3N, acetone, 80 °C, 8 h

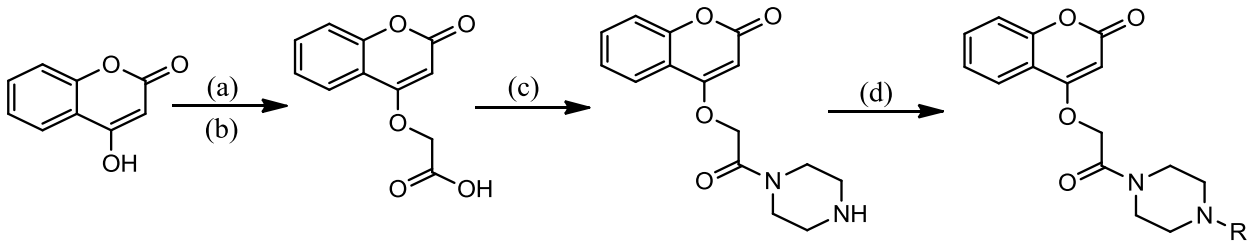
Scheme. 23:



Reagents and conditions: (a) K_2CO_3, DMF, reflux, 2-4 h

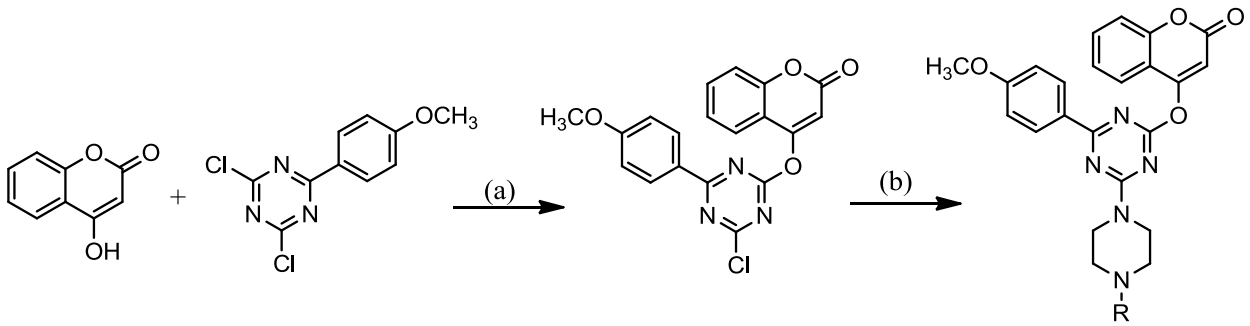
R = 6-CH_3, 7-CH_3, 5,7-$(CH_3)_2$, 6-OCH_3, 7,8-benzo, 6-tert butyl, 5,6-benzo, 6-Cl

Scheme. 24:



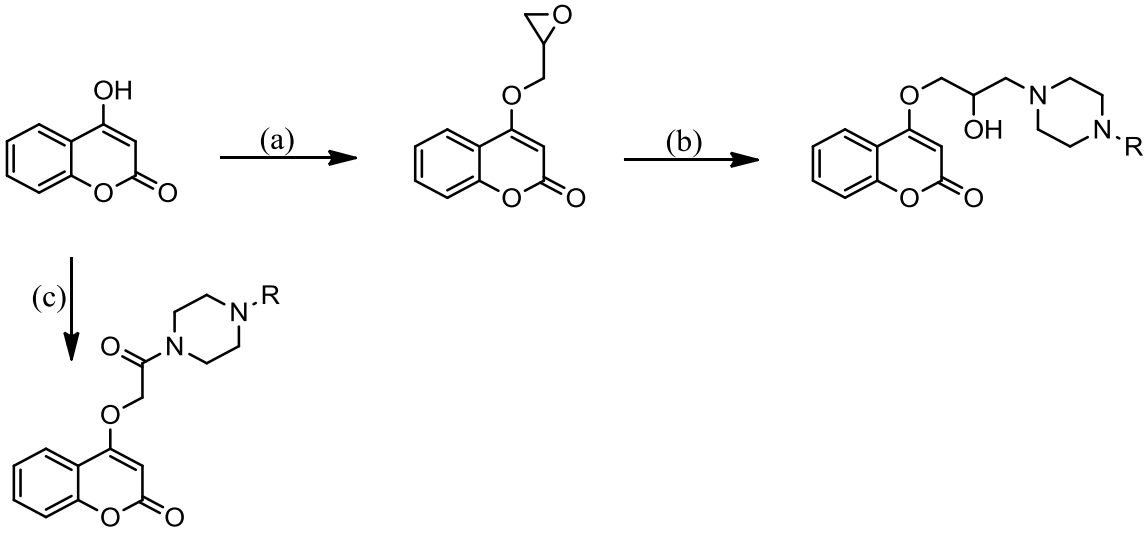
Reagents and conditions: (a) $BrCH_2COOEt$, K_2CO_3, DMF, 50-60 °C (b) LiOH, THF, H_2O, 0 °C, rt (c) piperazine, EDCI, HOBt, DIPEA, DMF, 25-30 °C (d) RCl, TEA, DCM, 0-5 °C

Scheme. 25:



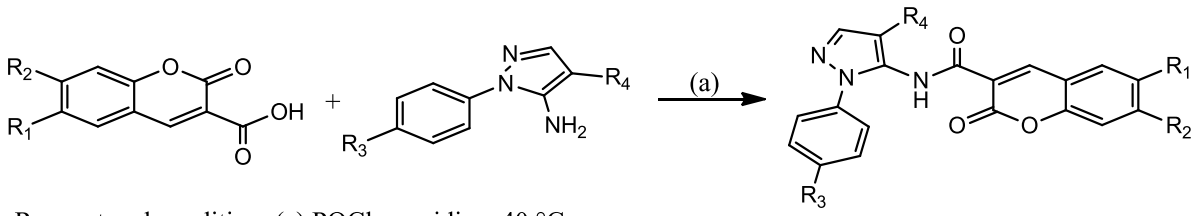
Reagents and conditions: (a) DMF, $NaHCO_3$, 40-45 °C (b) DMF, $NaHCO_3$, 80-90 °C
R = CH_3, C_2H_5, $COOC_2H_5$, $COCH_3$, C_6H_5, $CH_2C_6H_5$, $CH(C_6H_5)_2$

Scheme. 26:



Reagents and conditions: (a) Epoxy chloropropane, acetone, K_2CO_3, 50 °C, 10-12 h (b) substituted piperazine, K_2CO_3, DMF, 110 °C, 20-24 h (c) 2-Bromo-1-(4-methylpiperazin-1-yl)ethanone, CH_2Cl_2, HOBt, EDC, 50 °C, 8-12 h

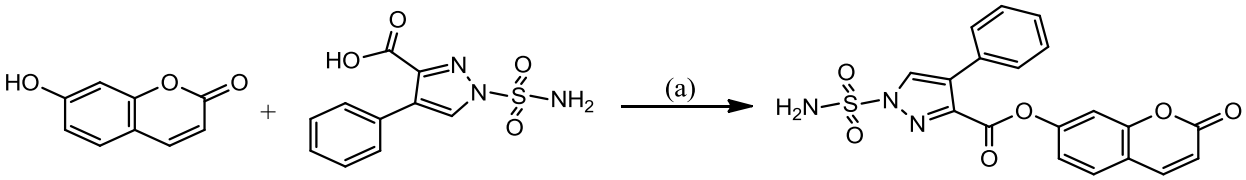
Scheme. 27:



Reagent and condition: (a) $POCl_3$, pyridine, 40 °C

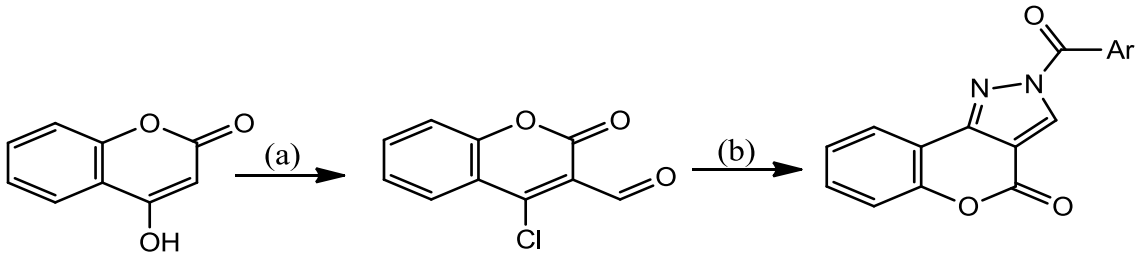
R_1 = H, Br, Cl, NO_2, CH_3; R_2 = H, $N(Et)_2$; R_3 = H, F, Cl, CH_3; R_4 = COOEt, COOH, CN

Scheme. 28:



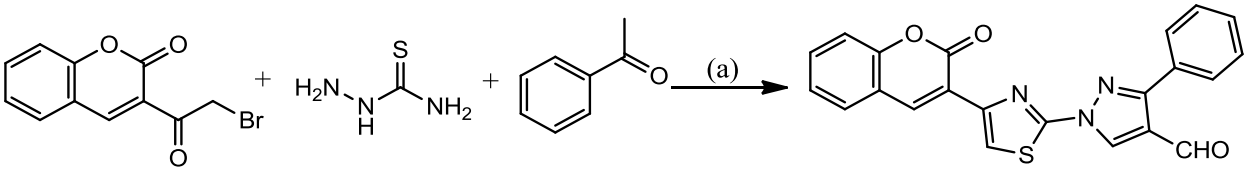
Reagents and conditions: (a) EDC, HCl, HOBt, DMAP, dichloromethane, rt, 24 h

Scheme. 29:



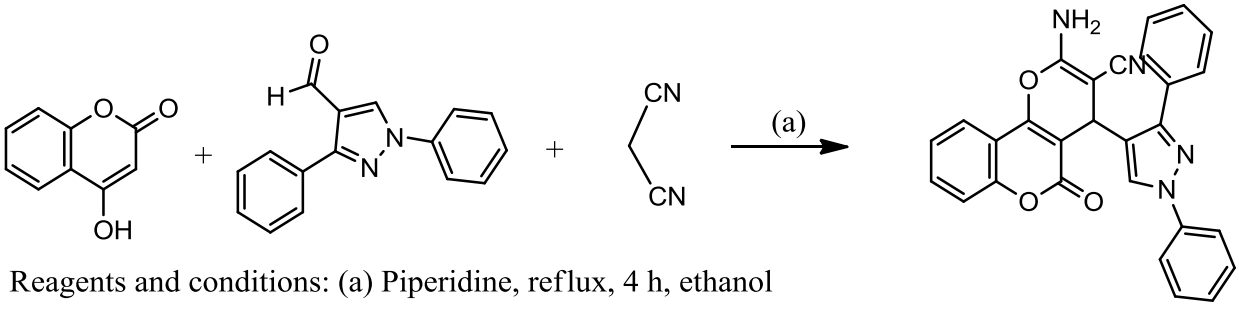
Reagents and conditions: (a) $POCl_3$, DMF, 60 °C(b) CH_2Cl_2/EtOH (1:3), rt, 15 min-1 h

Scheme. 30:



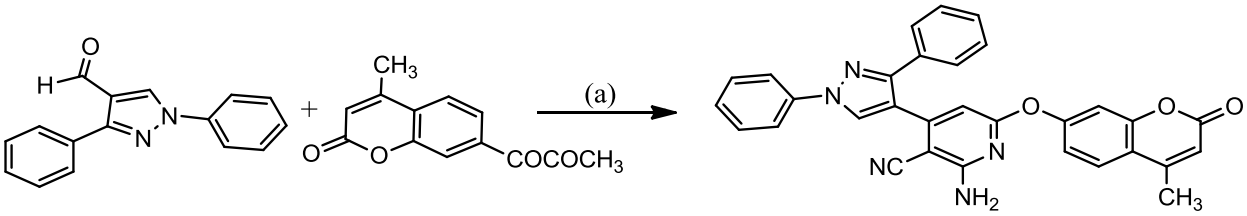
Reagents and conditions: (a) DMF, rt, stirring, $POCl_3$, 60 °C, 5-6 h

Scheme. 31:



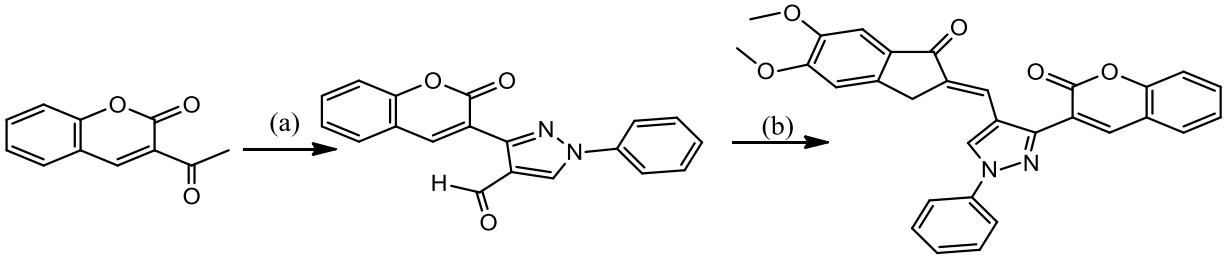
Reagents and conditions: (a) Piperidine, reflux, 4 h, ethanol

Scheme. 32:



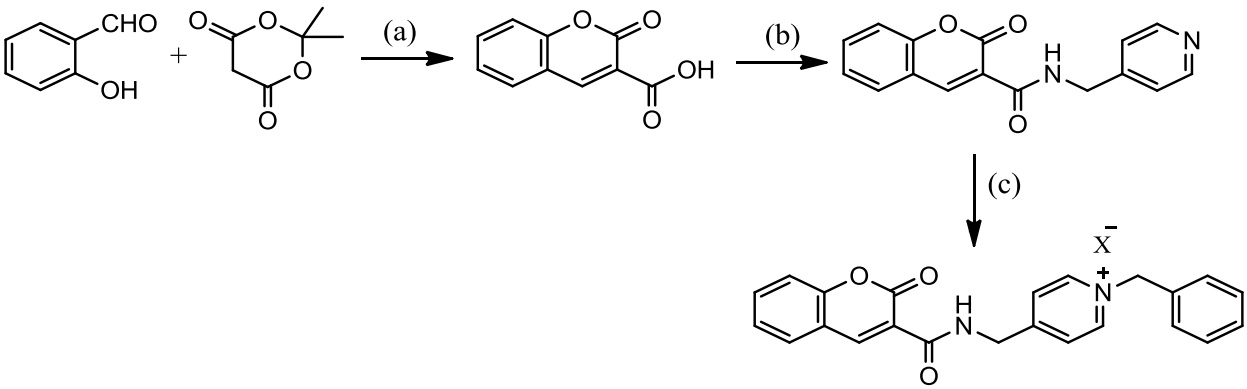
Reagents and conditions: (a) Malanonitrile, ammonium acetate, CH_3COOH, reflux, 3 h

Scheme. 33:



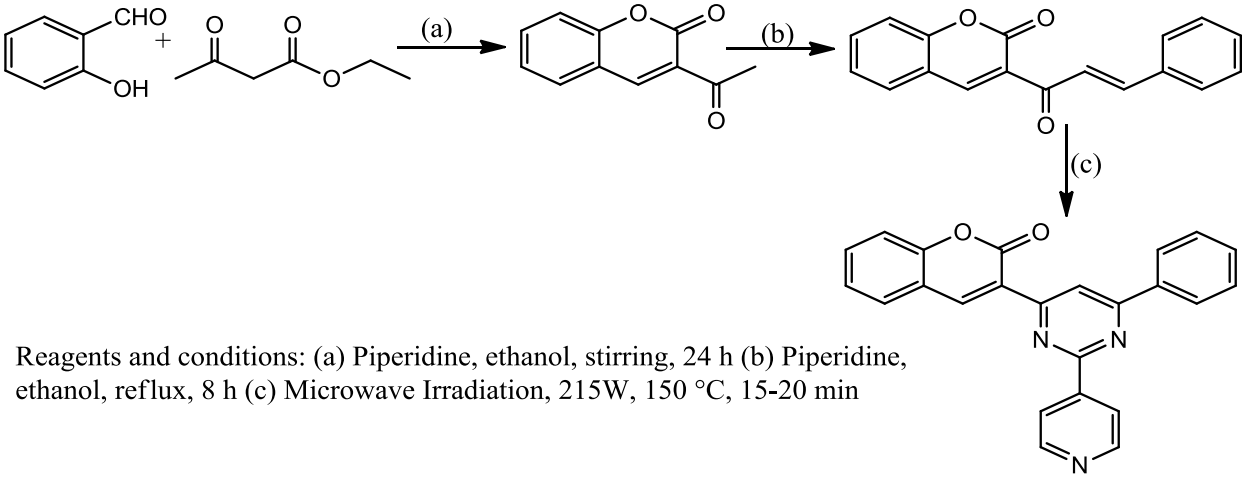
Reagents and conditions: (a) Phenyl hydrazine, CH_3COONa, ethanol and DMF, $POCl_3$ (b) 5,6-Dimethoxy-2,3-dihydro-1*H*-inden-1-one, methanol, NaOH

Scheme. 34:



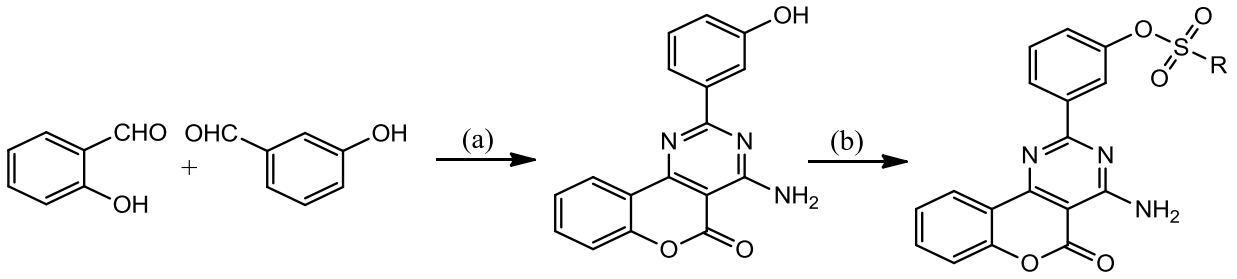
Reagents and conditions: (a) H_2O, rt, 4 h (b) Pyridin-3-yl methanamine or pyridin-4-yl methanamine, CH_3CN, HOBt, EDCl, 24 h (c) Benzyl halides, CH_3CN, reflux 3-4 h

Scheme. 35:



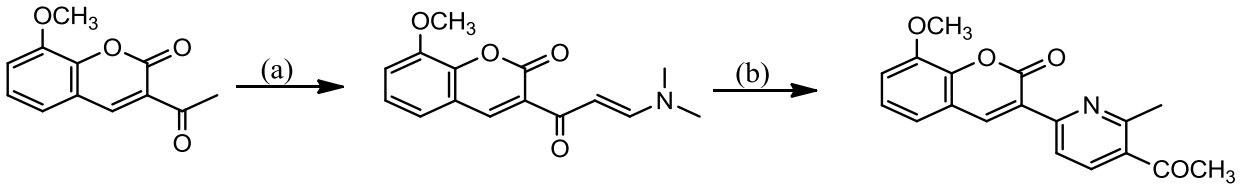
Reagents and conditions: (a) Piperidine, ethanol, stirring, 24 h (b) Piperidine, ethanol, reflux, 8 h (c) Microwave Irradiation, 215W, 150 °C, 15-20 min

Scheme. 36:



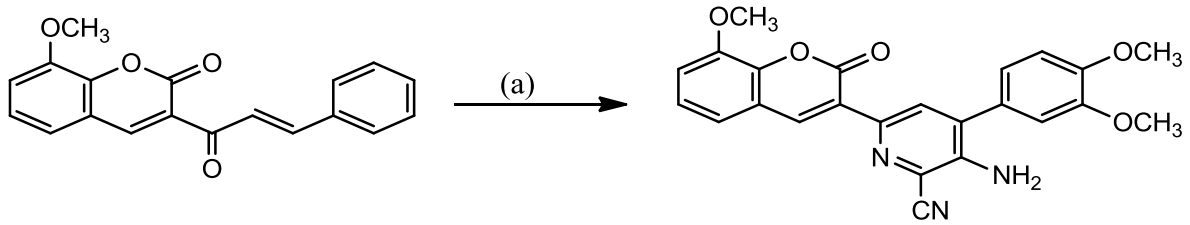
Reagents and conditions: (a) $CNCH_2COOC_2H_5$, NH_4OAc, C_2H_5OH, reflux, 2 h (b) $ClSO_2R$, DMF, rt, 2 h

Scheme. 37:



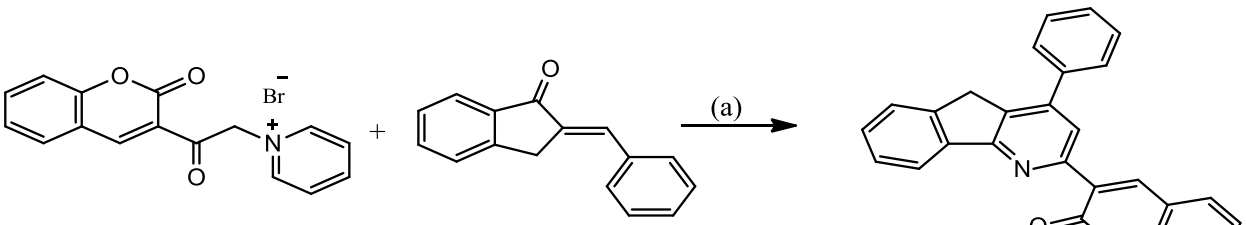
Reagents and conditions: (a) DMF-DMA, toluene, reflux, 12 h (b) Acetyl acetone or ethyl acetoacetate, ammonium acetate, glacial acetic acid, reflux, 4 h

Scheme. 38:



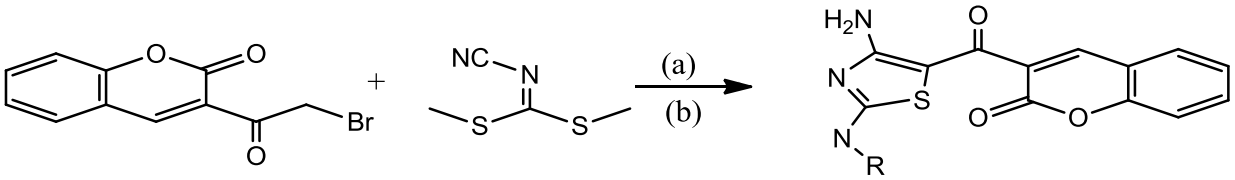
Reagents and conditions: (a) malononitrile, ammonium acetate, glacial acetic acid, reflux 4-6 h

Scheme. 39:



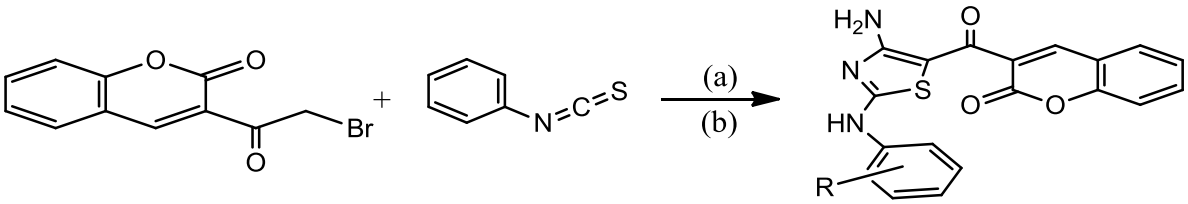
Reagents and conditions: (a) NH_4OAc, glacial acetic acid, 140 °C

Scheme. 40:



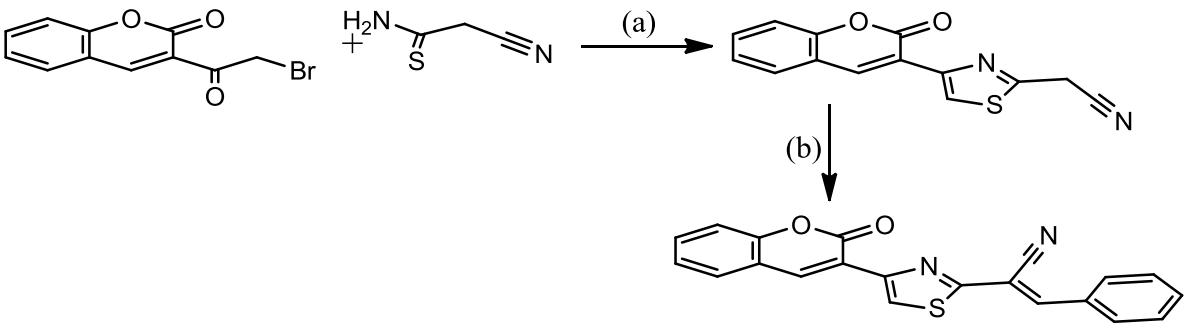
Reagents and conditions: (a) Appropriate cyclic amine, DMF, 70 °C, 1 h and $Na_2S.9H_2O$ 60 %, 70 °C, 2 h (b) 0-5 °C, 2 h

Scheme. 41:



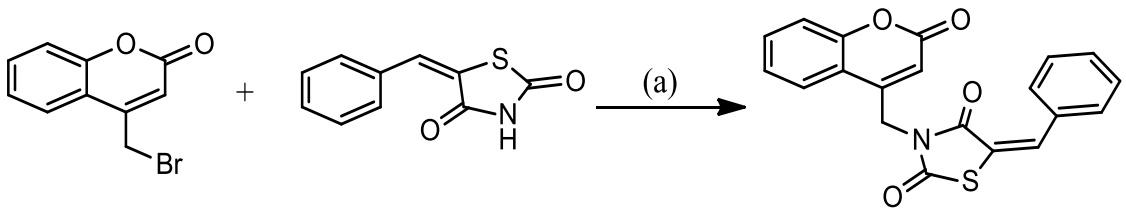
Reagents and conditions: (a) NH_2CN, CH_3OH, 0-5 °C, 1 h and Na/CH_3OH, 0-5 °C, 2 h (b) 0-5 °C, 2 h

Scheme. 42:



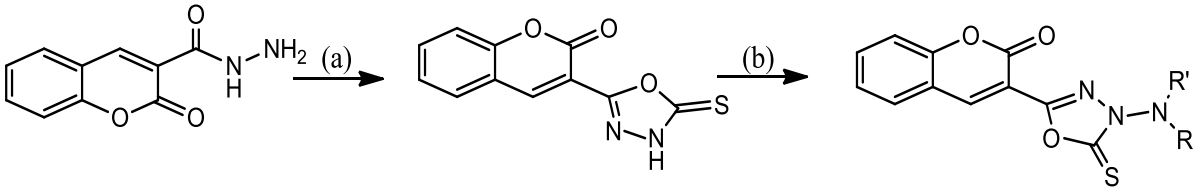
Reagents and conditions: (a) Methanol, reflux, 3 h (b) Methanol, reflux, 2.5 h

Scheme. 43:



Reagents and conditions: (a) Anhyd. K_2CO_3, acetone, M.W. 100W, 50 °C, 5-9 min

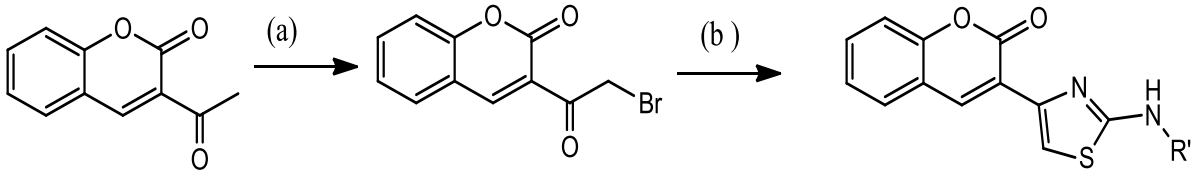
Scheme. 44:



Reagents and conditions: (a) KOH, CS_2, reflux (b) Ethanol, reflux

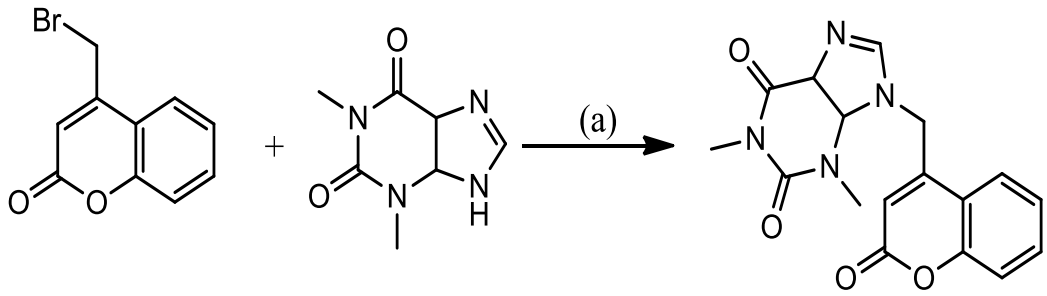
R = H, morpholine, C_6H_5 R' = 4-CH_3, n Bu, 2-ClC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, morpholine, C_6H_5

Scheme. 45:



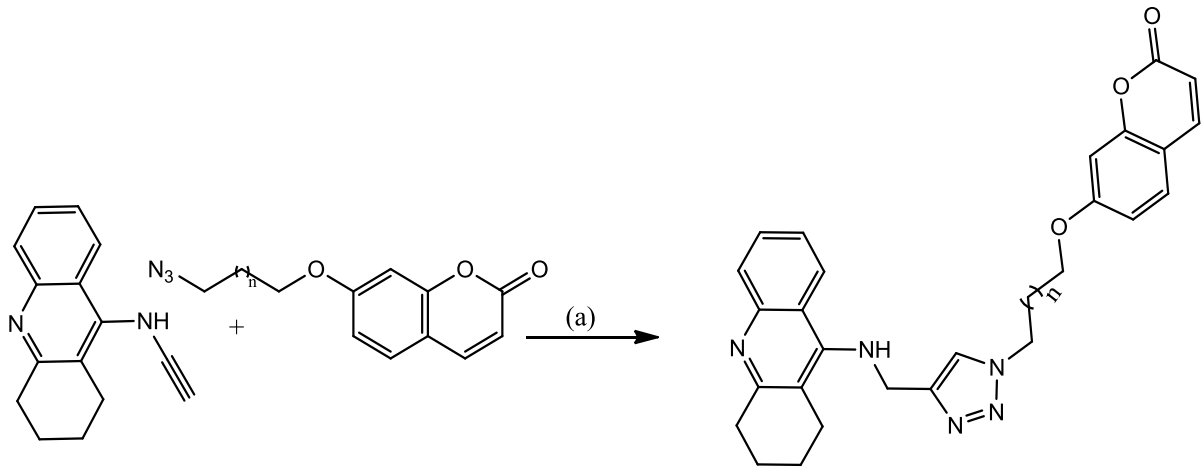
Reagents and conditions: (a) Br_2, $CHCl_3$, 0-5 ºC stirring, 4-5 h (b) $CHCl_3$, EtOH (2:1), reflux, 3 h

Scheme. 46:



Reagents and conditions: (a) Activated K_2CO_3, acetone, rt, 6-8 h

Scheme. 47:



Reagents and conditions: (a) CuI, H_2O/t-BuOH, Et_3N, 12-24 h

Scheme. 48:

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