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REVIEW

Synthetic Methodologies and Pharmacological Significance of 2-Aminobenzophenones as Versatile Building Block

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ABSTRACT

2-Aminobenzophenones are imperative chemical compounds in medicinal chemistry because of their application as valuable synthon for the synthesis of wide varieties heterocyclic compounds having versatile biological activities. Thus, over the past decades, medicinal chemists are increasing attracted towards exploring various synthetic routes and methodologies for the synthesis of 2-aminobenzophenone and its derivatives. This mini-review covers some of the finest methods for the synthesis of 2-aminobenzophenone as well as biological activities of its novel derivatives. The review also discusses the various bioactive compounds in which 2-aminobenzophenones were used as a precursor.

KEYWORDS

2-Aminobenzophenone, 2-Aminobenzonitrile, 2-Benzoylbenzoic acid, Anthranilic acid.

INTRODUCTION

2-Aminobenzophenone derivatives are important compounds in organic chemistry because of their applications in heterocyclic synthesis and medicines [1]. It is valuable synthon for the synthesis of various heterocyclic systems, such as fluorenones, acridines, acridones, quinazolines, quinolines, indazoles and 3-arylindoles [2-5], tetrahydroquinolines [6], quinazolines [7], 1,2-dihydroquinazolines [8,9], 2,3-disubstituted indoles [10], 3,3-dimethyl-9-phenyl-3,4-dihydroacridin-1(2*H*)-one [11], dibenzodiazepines [12] and benzodiazepin-2-one [13]. Furthermore, 4-arylquinazolones, 4-arylquinolines, 4-arylquinoline-2-ones, polyphenylquinolines and 1, 4-benzodiazepines have been prepared from 2-aminobenzophenone. The pharmacological activity of 2-aminobenzophenone is the most important focus in the study of the preparation of 2-aminobenzophenone derivatives [14]. Several drugs possessing high pharmaceutical activity, such as chlorodiazepoxide (clinical psychosis), proquazone and amfenac (anti-inflammatory agents) have been prepared from 2-aminobenzophenone [15-17]. They are also used as starting materials for the preparation of the antidepressant drug tampramine [18] and tetradentate Schiff-base ligands [19]. Their synthesis is difficult because they have both amino and carbonyl active groups in the position *ortho* to benzene ring. There are various synthetic strategies which are reported in literature for the preparation of substituted 2-aminobenzophenones.

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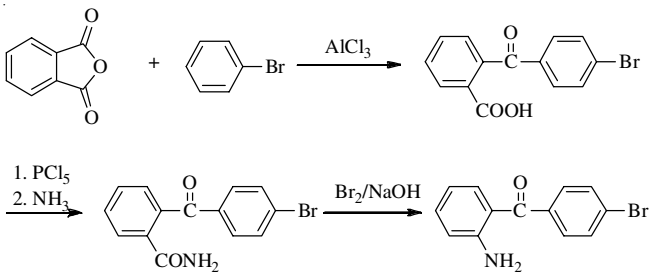
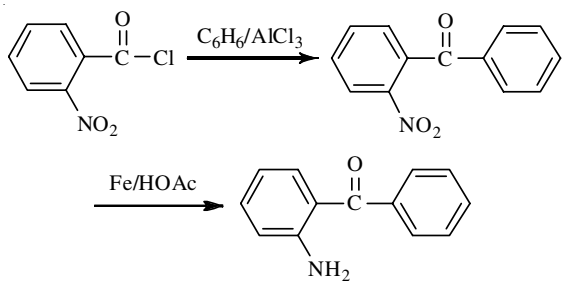
Synthesis of 2-aminobenzophenones: There are some general methods for the preparation of 2-aminobenzophenone, such as Friedel-Crafts reaction of anthranilic acid derivatives with aryl compounds, Friedel-Crafts acylation of *para* -substituted anilines, and reaction of aryl-Grignard reagents with 2-nitro or 2-aminobenzaldehydes. These methods are common, but contain several additional steps, such as protection and deprotection of the amino group. The continued discovery of novel heterocyclic rings with new biological activities makes versatile routes for the synthesis of 2-aminobenzophenones.

Synthesis from 2-benzoylbenzoic acids: It involves a Hofmann rearrangement of an amide or a Curtius reaction. The yields are good (83%), but several steps are required to obtain the desired product. This procedure is limited by the availability of substituted phthalic anhydride starting material and by regioselectivity of Friedel-Crafts acylation [1,20] (**Scheme-I**).



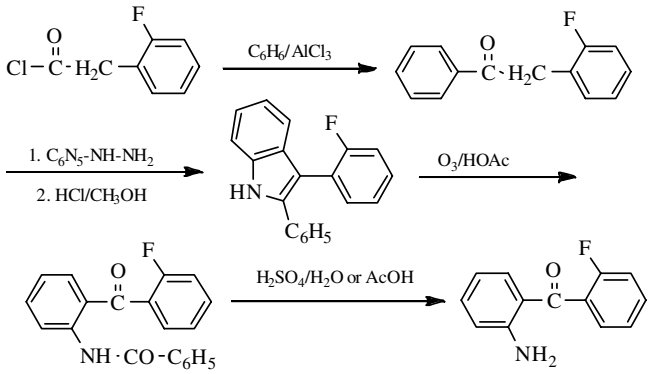
Scheme-I

Synthesis from nitrobenzoyl chloride: It involves Friedel-Crafts reaction of 2-nitrobenzoyl chloride with benzene or substituted benzene. Reduction of intermediate nitrobenzophenone affords the corresponding aminobenzophenones. The drawback of this reaction is 2-nitrobenzoyl chlorides are not good substrates for Friedel-Crafts reaction, probably due to detrimental complexation of nitro group with the catalyst [1] (**Scheme-II**).



Scheme-II

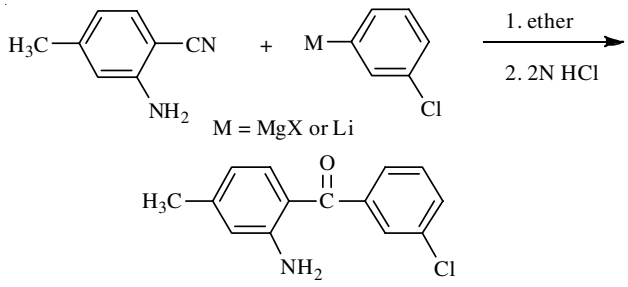
Synthesis from 3-arylindoles: 3-Arylindoles are used for the preparation of 2-substituted 2-aminobenzophenones. Yields are excellent, being about 60 % overall from *o*-fluorophenylacetyl chloride [21] (**Scheme-III**).



Scheme-III

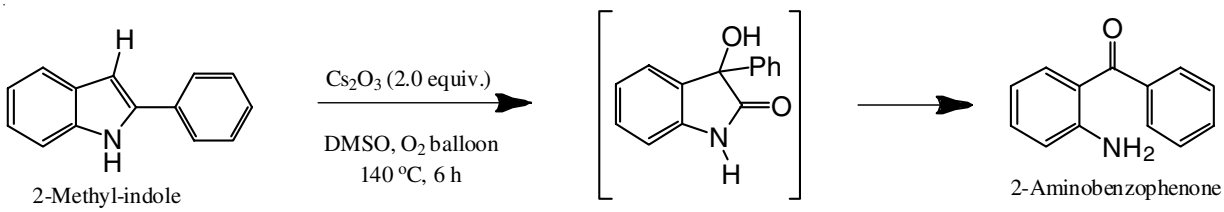
Yu *et al.* [22] synthesized various 2-aminobenzophenones from readily available 2-arylindoles in DMSO under O_2 balloon atmosphere. The synthesis was carried out under transition metal-free conditions without the use of air-sensitive organometallic reagents. The maximum yield (60 %) of 2-aminobenzophenone is obtained in presence of Cs_2CO_3 (2 equiv.) in DMSO solvent at 140 °C for 6 h [22] (**Scheme-IV**).

Synthesis from 2-aminobenzonitrile: The reaction of 2-aminobenzonitriles with aryl-Grignard or lithium reagents leads to 2-aminobenzophenones in good yields (71 %) [14] (**Scheme-V**). In another method, Chen *et al.* [23] synthesized 2-aminobenzophenone by palladium catalyzed addition of sodium arylsulfinates to unprotected 2-aminobenzonitriles. In this method, a new strategy for constructing *o*-aminobenzophenones was described. Mechanism of the reaction involves desulfination and addition reaction. Sodium arylsulfinates are relatively stable, easy to handle and used as aryl source in transition metal catalyzed desulfinative reactions [23]. The method represents a convenient and practical strategy for synthesis of *o*-aminobenzophenones (**Scheme-VI**).

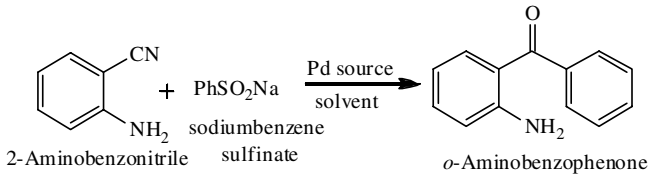


Scheme-V

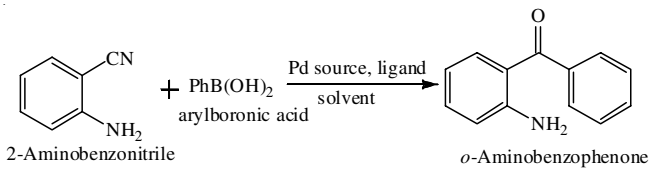
The same group in 2014 [24], described a palladium catalyzed synthesis of 2-aminobenzophenone. In this reaction direct addition of arylboronic acid to 2-aminobenzonitrile derivatives leads to a wide range of 2-aminobenzophenones with excellent yields [24] (**Scheme-VII**).



Scheme-IV

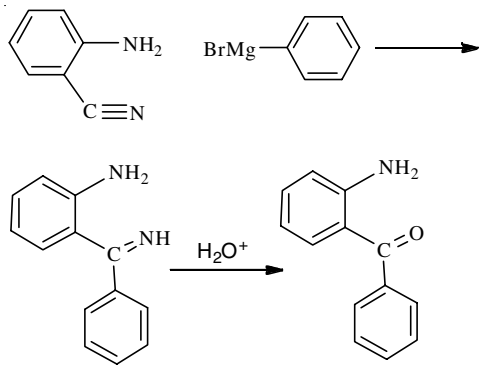


Scheme-VI



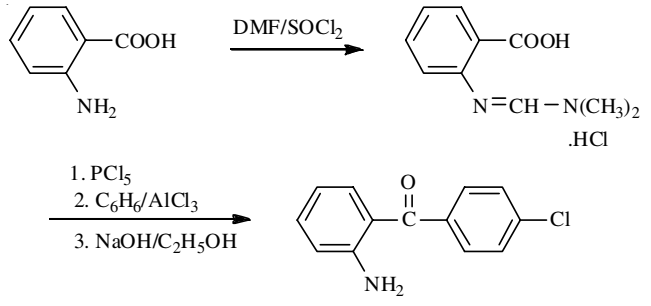
Scheme-VII

Mateos *et al.* [25] synthesized 2-aminobenzophenone ring by reacting Grignard reagent with 2-aminobenzonitrile. This transformations was achieved *via* nucleohilic addition of Grignard reagent to 2-aminobenzonitrile resulting in the formation of corresponding imine salt intermediate, which underwent hydrolysis by means of in-series plug flow reactors leading the formation of 2-aminobenzophenones. Since the ketone is not formed until after the addition of water, the organo-metallic reagent doesnot get the chance to react with ketone product [25] (**Scheme-VIII**).



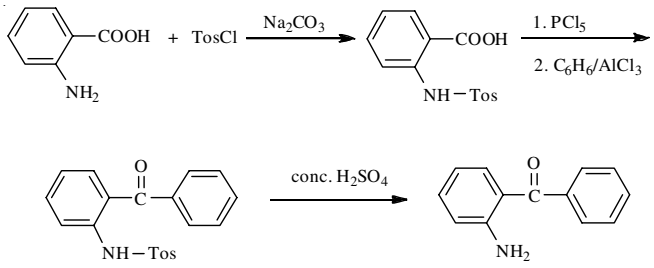
Scheme-VIII

Synthesis from anthranilic acid: The amino group in anthranilic acid can be protected to give 2-aminobenzophenone by forming an amidine adduct with dimethyl formamide. The acid chloride is formed *in situ* and then will undergo a Friedel-Crafts reaction (**Scheme-IX**). The yields are moderate (40-60 %) [1,26].



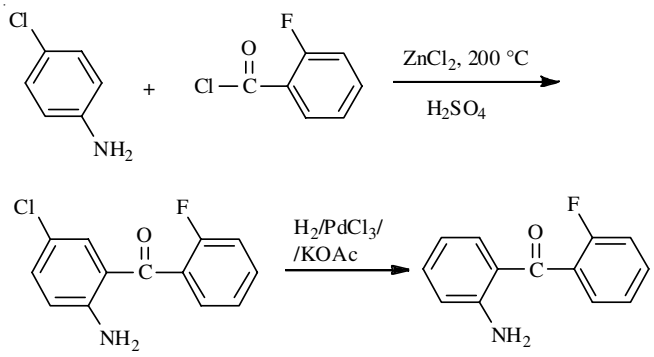
Scheme-IX

In another method, amino group in anthranilic acid is protected with *p*-toluenesulfonyl chloride. The acid chloride is prepared and used in a Friedel-Crafts reaction to give moderate yields of products. One drawback to this method is that sulfonamide bond is quite stable and rigorous acidic conditions are required for removal of the protecting group [1] (**Scheme-X**).



Scheme-X

Synthesis from aniline by *para*-substitution: A Friedel Crafts acylation or alkylation of aniline results in substitution *para* to amine function. If *para* position is already substituted, then the group will be introduced *ortho* to the amine and 2-aminobenzophenone can be obtained in moderate yields. When the *para*-substituent is chlorine or bromine, it can be removed by hydrogenolysis to give unsubstituted 2-aminobenzophenones. The conditions required for Friedel-Crafts reaction are quite vigorous [27] (**Scheme-XI**).

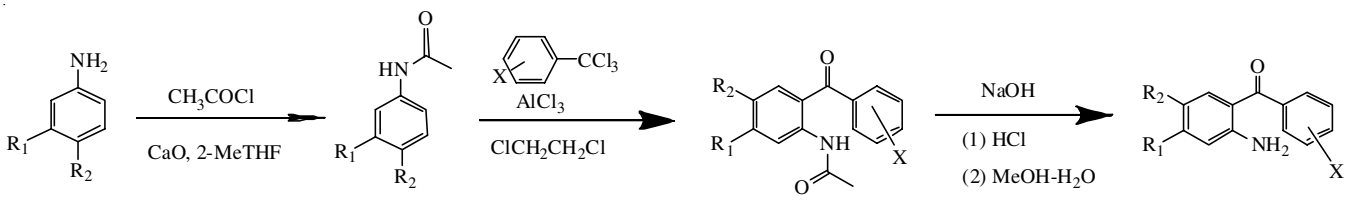


Scheme-XI

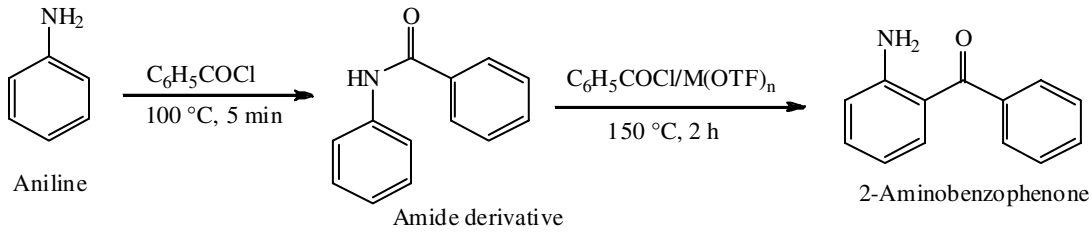
Ma *et al.* [28] synthesized 2-aminobenzophenone from substituted anilines. It involves three steps reaction. In the first step, aniline was acetylated with acetyl chloride in the presence of 2-MeTHF and CaO to give acetanilides. Then these acetanilides are benzoylated with (trichloromethyl)benzene in presence of aluminium to give 2-acetamidobenzophenone. In the last step, the removal of acetyl group from amino group provides the substituted 2-aminobenzophenone [28] (**Scheme-XII**).

Tran *et al.* [29] described an efficient pathway for the synthesis of aminobenzophenone derivatives *via* Friedal-Craft benzoylation using copper triflate as catalyst that also include three steps reaction *i.e.* (i) synthesis of amide derivatives, (ii) Friedal-Craft benzoylation reaction, and (iii) hydrolysis of amide derivatives in acridic acid solution [30] (**Scheme-XIII**).

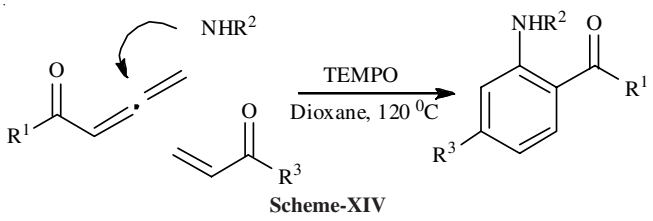
Recently, Tian *et al.* [30] reportd a TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl]-dependent tunable synthesis of functionalized cyclohexa-1,3-dienes and 2-aminobenzophenones/benzoate from the one-pot cascade reactions of allenic ketones/allenoate with amines and enones [30] (**Scheme-XIV**).



Scheme-XII

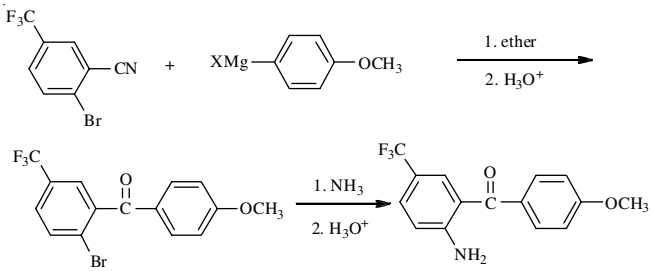


Scheme-XIII



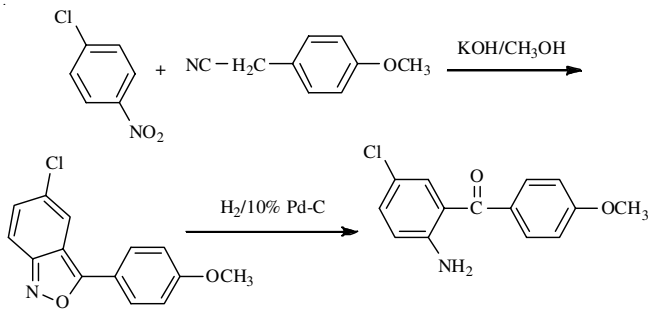
Scheme-XIV

Synthesis from 2-halobenzophenones: Several trifluoromethyl derivatives of 2-aminobenzophenones have been prepared by displacement of an activated halogen by ammonia from 2-halobenzophenone [31] (**Scheme-XV**).



Scheme-XV

Synthesis from 2,1-benzisoxazoles: 2-Aminobenzophenones may be obtained by chemical or careful catalytic reduction of 2,1-benzisoxazoles (anthranils) [32]. Some limitations for their preparation are that nitrobenzene derivative must be substituted in the *para* position and certain substituents such as methyl and methoxy, are incompatible with the reaction conditions [33] (**Scheme-XVI**).



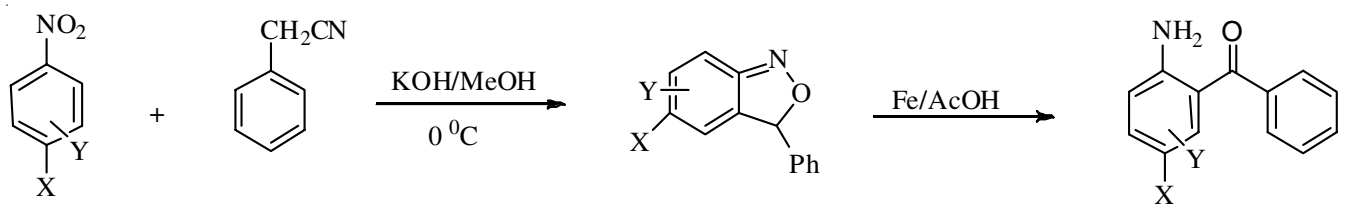
Scheme-XVI

Ghomi *et al.* [34] described a quick and convenient method for the preparation of 2-aminobenzophenone derivatives. This approach consists of the nucleophilic substitution reaction of nitrobenzenes by phenylacetonitrile under conventional and ultrasonic conditions followed by reduction of produced 2,1-benzisoxazole to 2-aminobenzophenone. This 2-step reaction was studied by changing the reaction parameters (reaction temperature, ultrasound power and reaction time). The results clearly demonstrated that using ultrasound irradiation results in a high yield within a short reaction time [34] (**Scheme-XVII**).

Biological activities of 2-aminobenzophenone derivatives:

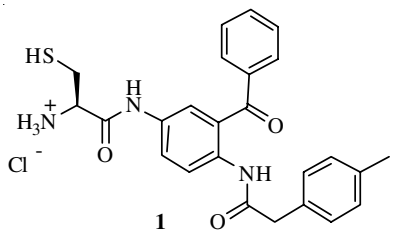
2-Aminobenzophenone and its derivatives are known to be associated with a wide variety of biological and pharmacological properties. We will restrict to present study to the important development in the pharmacological activities of 2-aminobenzophenone derivatives.

Sakowski *et al.* [35] described the structure-activity relationship of a novel class of CAAX-peptidomimeticfarnesyltransferase inhibitors based on benzophenone scaffold. 4′-Methyl,



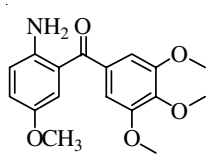
Scheme-XVII

4′-chloro, 4′-bromo and 4′-nitrophenylacetic acid as substituents at 2-amino group of the benzophenones core structure yield farnesyltransferase inhibitors that were active in the nano molar range. Flex docking of compound **1** confirmed the good fit of the molecule into the peptide binding site of farnesyltransferase [35].



1

Hsieh *et al.* [36], carried out the structure-activity and crystallographic analysis of benzophenones derivatives. Compounds **2-5**, showed excellent cytotoxic activities against a panel of human cancer cell lines including multi-drug resistant cell lines. The X-ray three-dimensional structural analysis shows that proton donor in B ring may be required for cytotoxic activity, with intermolecular hydrogen bonding playing an important role [37].



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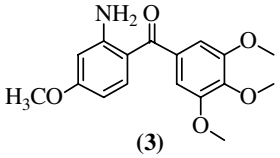

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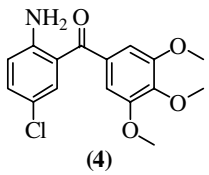

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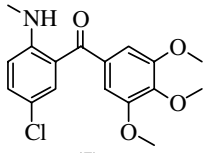
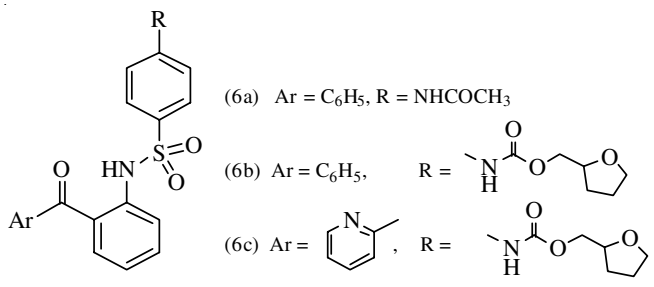


(5)

In an attempt of finding potent B1 receptor antagonist, Su *et al.* [38] carried out the structure activity relationships (SAR) of the structurally novel 2-aminobenzophenones. It has been reported that compound **6a** was potent hBK B1 receptor antagonist with excellent receptor occupancy in the CNS of hBK B1 transgenic rats but not a substrate for P-glycoprotein (P-gp) mediated efflux and not a potassium channel blocker [37]. Compound **6b** displays sub nano molar binding affinity for hB1 receptor and possessed a good profile for P-gp efflux. Compound **6c** showed a balanced profile in terms of potency and P-gp susceptibility [38].



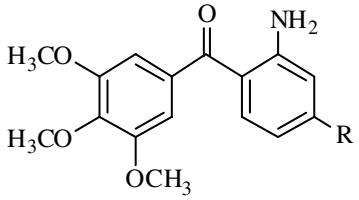
(6a) Ar = C_6H_5, R = $NHCOCH_3$

(6b) Ar = C_6H_5, R =

(6c) Ar = , R =

6a-c

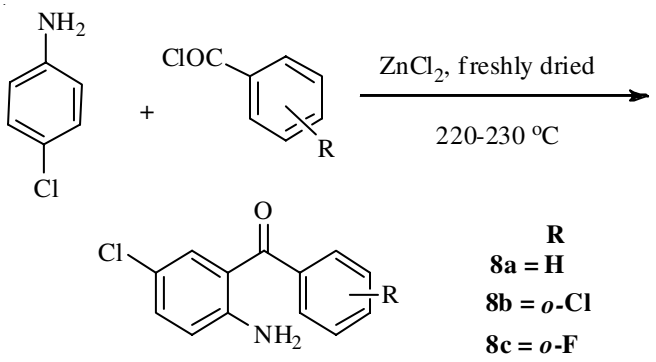
A new type of inhibitor of tubulin polymerization was discovered on the basis of the combretastain molecular skeleton. The lead compounds in this series, compounds **7a** and **7b**, strongly inhibited tubulin polymerization *in vitro* and significantly arrested cells at the G2/M phase. Compounds **7a** and **7b** yielded 50- to 100-fold lower IC_{50} values than did combre-tastain A-4 against Colo 205, NUGC3 and HA22T human cancer cell lines as well as similar or greater growth inhibitory activities than did combretastain A-4 against DLD-1, HR, MCF-7, DU145, HONE-1 and MES-SA/DX5 human cancer cell lines [39]. Structure activity relationship information revealed that introduction of an amino group at the *ortho* position of benzophenones ring plays an integral role for increased growth inhibition [39].



7a, R=4OCH_3
7b, R=5-OCH_3

7a-b

Maya *et al.* [40] synthesized a number of 2-aminobenzophenones by acylation of *para*-chloroaniline with different 2-, 3-, 4-chloro- or fluorobenzoyl chloride in solid state *via* Friedel-Crafts reaction as shown in **Scheme-XVIII**. Evaluation of biological activity *in vitro* showed that the selected compounds **8a**, **8b** and **8c** have potential anticancer activity. The presence of one chlorine atom in the second aromatic ring of benzophenones molecule makes it more active [40].

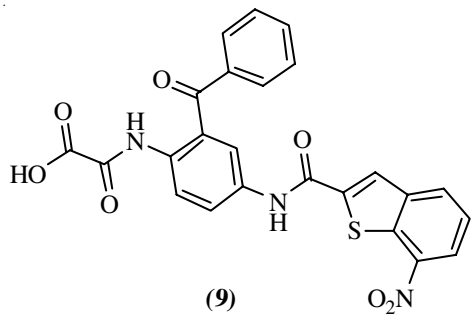


R
8a = H
8b = *o*-Cl
8c = *o*-F

8a-c

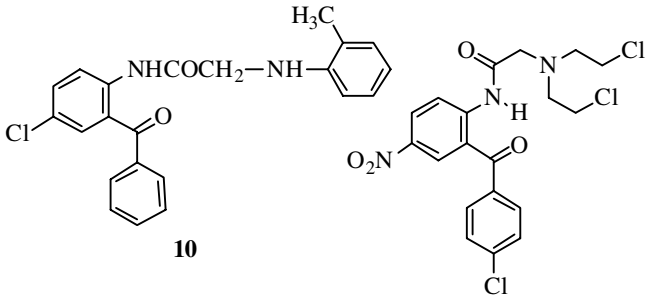
Scheme-XVIII

A series of novel benzophenones-based chemical entities were synthesized and evaluated as potent Pin1 (protein interaction with NIMA1) inhibitors. Of all the synthesized compounds, the most active compound was compound **9** with an IC_{50} value of 5.99 μmol/L. From SAR studies, it was found that aromatic hydrophobic fragments at position 4 exhibited varied inhibitory activities on Pin1 with an IC_{50} value ranging from 5.99 μM to 18.30 μM. Among which, 7-nitro benzothiophene moiety is the most favourable variations and lead to inhibitory activities with an IC_{50} value of 5.99 μM. When 4-aromatic group was replaced by acetyl substituent, the inhibition effect was completely lost [41].



(9)

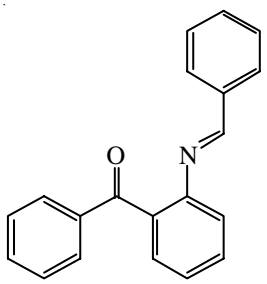
A series of novel 2-amino-5-chlorobenzophenone derivatives were prepared. The compounds were screened for the skeletal muscle relaxant activity. It was quite apparent that all 2-amino-5-chlorobenzophenone derivatives possess significant differences between control group and treated group ($p < 0.001$). Among these 2-amino-5-chlorobenzophenone derivatives, compound **10** bearing *o*-toluidine as a substituent possesses the highest skeletal muscle relaxant activity [42]. Singh *et al.* [43] synthesized a series of novel substituted aminobenzophenones derivatives containing nitrogen mustard moiety. Most of the compounds showed potent antitumor activity, compound **11** displayed the highest activity against CNS cancer cell line [43].



10

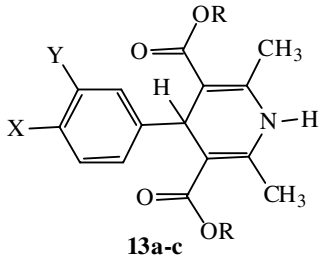
11

Fareed *et al.* [44] synthesized a novel series of Schiff bases from condensation of 2-aminobenzophenone with the different carbonyl compounds in the presence of dodecatungstolicic acid/P_2O_5 in the solvent free conditions. Compound **12** which is less sterically hindered as compared to all screened compounds showed 51 % antioxidant activity due to its low steric hindrance [44].

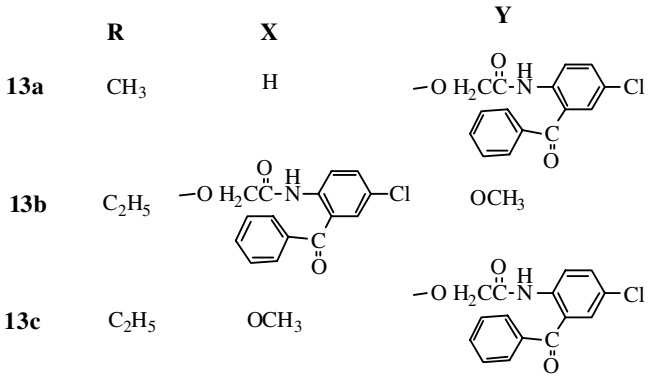


12

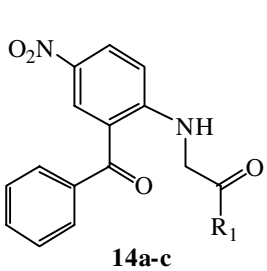
Li *et al.* [45] synthesized a series of novel aminobenzophenones linked 1,4-dihydropyridines (1,4-DHPs) hybrids. The combination of two pharmacophore *i.e.* aminobenzophenones and 1,4-dihydropyridines gives synergistic effect. The final compounds were prepared by two methods. Method A includes stirring at room temperature of 2-(chlorocetamido)-5-chlorobenzophenone substituted 1,4-dihydropyridines in the presence of potassium carbonate and sodium iodide in a minimum quantity of DMF. Method B includes refluxing of compound and substitute 1,4-dihydropyridines in ethyl methyl ketone as solvent in the presence of potassium carbonate as catalyst. The compounds **13a**, **13b** and **13c** were found to be most active against antibacterial studies [45].



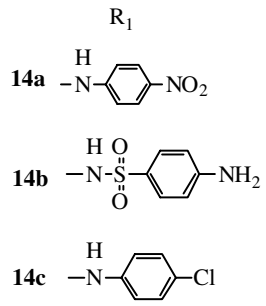
13a-c



Li *et al.* [46] synthesized various 2-amino-5-nitrobenzophenone derivatives by conventional and microwave irradiation method. The antibacterial activities of synthesized compounds were evaluated and compounds **14a-c** were found to be highly active [46].

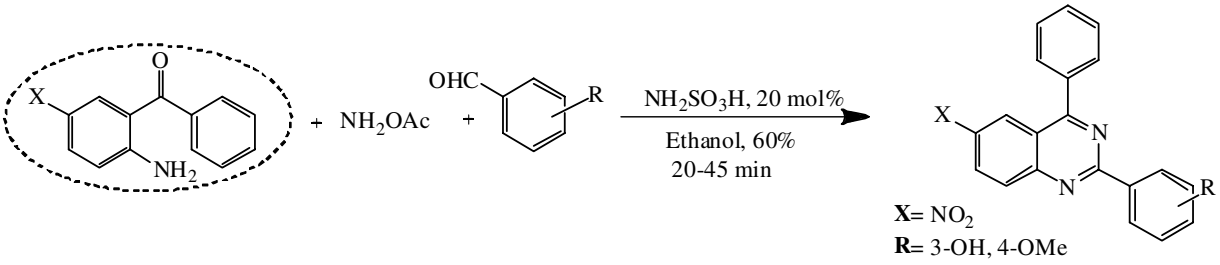


14a-c

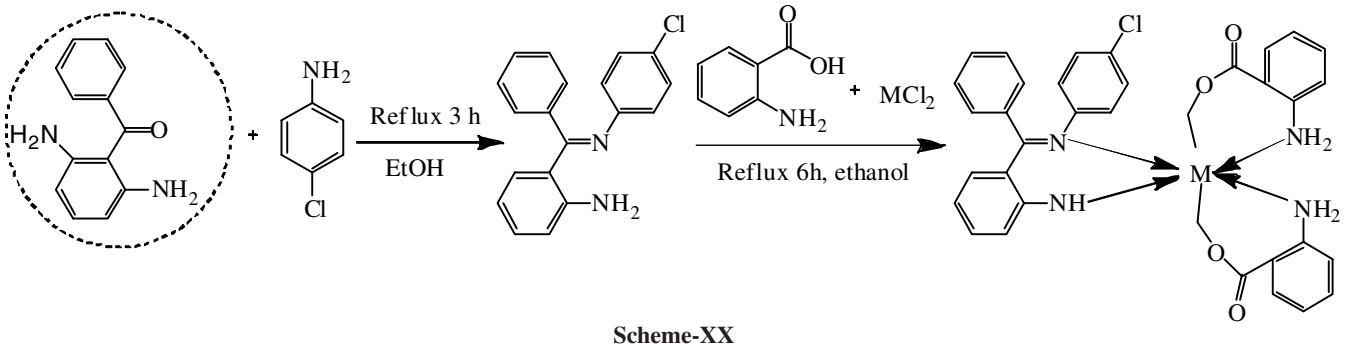


2-Aminobenzophenone as synthetic precursors

Kamal *et al.* [47] synthesized a series of derivatives of 1,2-dihydroquinazolines. These derivatives were formed by the reaction between aromatic aldehydes, 2-aminobenzophenones, and ammonium acetate with sulfamic acid as a green and recyclable catalyst. It was observed that aromatic aldehydes with both electron donating as well as electron withdrawing substituents react well, providing good yields (81-96 %) of the corresponding products. All the derivatives were tested for antimicrobial activity against both gram-positive and gram negative bacterial strains as well as a fungal strain [47] (**Scheme-XIX**).



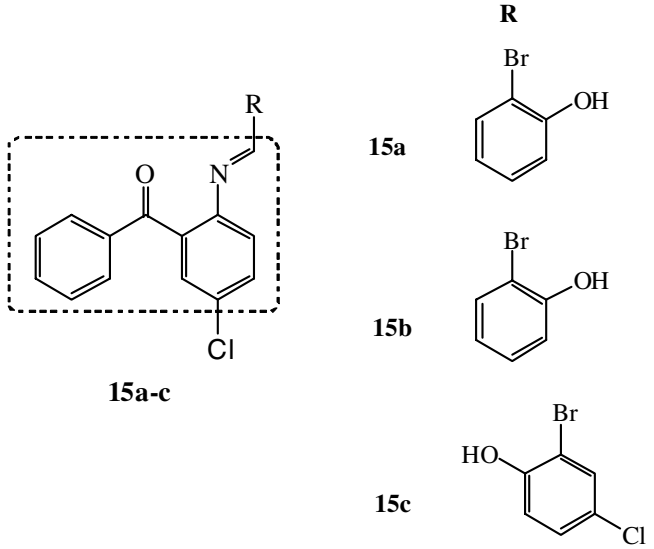
Scheme-XIX



Scheme-XX

Muniyandi *et al*. [48] prepared four bidentate complexes from 2-aminobenzophenone and characterized. The interaction of these complexes with CT-DNA has been explored by UV-absorption, fluorescence, viscosity, cyclic voltammetry (CV) and circular dichroism (CD) techniques which prove that the complex could bind to CT-DNA through intercalation. The oxidative cleavage with pbr322 DNA has also been investigated by gel electrophoresis catalytic activity of complexes has been evaluated towards the oxidation of aniline [48] (**Scheme-XX**).

Khan *et al*. [49] described the antibacterial/antibiofilm activities of microwave assisted synthetic 2-amino-5-chlorobenzophenone Schiff bases against four bacterial strains *i.e*. *Klebsellia pneumoniae*, *Proteus mirabilis*, *Staphylococcus aureus* and *Streptococcus mutans*. SAR of 2-amino-5-chlorobenzophenone Schiff bases described that different substitution at aryl part of the synthetic compounds was responsible for the inhibitory action. Three compounds *i.e*. **15a**, **15b** and **15c** showed potent biofilm disrupting properties [49].



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