4. Results and Discussion

The work carried out towards achieving the proposed plan has been discussed under the following two main headings:

1. Chemical Studies
2. Biological Studies

4.1 Chemical Studies

To synthesize the envisaged compounds research schemes were planned and discussed under the following headings:

4.1.1. Synthesis of 1,2-diaryl-1,2-ethanedione derivatives

4.1.1.1. Synthesis of substituted phenylacetic acids **(3,6,9,11)**

4.1.1.2. Synthesis of substituted diarylethanones **(15-32)** by Friedel-Craft acylation

4.1.1.3. Oxidation of substituted diarylethanones to obtain diketo compounds **(33-50)**

4.1.2. Synthesis of 2-substituted 4,5-diaryl-1*H*-imidazole derivatives

4.1.2.1. Synthesis of 2-(4-chlorophenyl)-4,5-diaryl-1*H*-imidazoles **(52a-68a)**

4.1.2.2. Synthesis of 2-(4-fluorophenyl)-4,5-diaryl-1*H*-imidazoles **(52b-68b)**

4.1.3. Synthesis of 5,6-diaryl-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine derivatives

4.1.3.1. Synthesis of 5,6-diaryl-3-methylthio-1,2,4-triazines **(70-82** and **83-92)**

4.1.3.2. Synthesis of *N*-(2-morpholinoethyl)-1,2,4-triazin-3-amines **(94-110)**

4.1.4. Synthesis of 2- and 7-substituted 4*H*-benzo[*d*][1,3]oxazin-4-one derivatives

4.1.4.1. Synthesis of 2-substituted 4*H*-benzo[*d*][1,3]oxazin-4-ones **(127a-141a)**

4.1.4.2. Synthesis of 7-chloro-2-substituted 4*H*-benzo[*d*][1,3]oxazin-4-ones **(127b-141b)**

4.1.5. Synthesis of guanido derivatives of anthranilamide

4.1.5.1. Synthesis of 2-substituted *N*-amidinobenzamides **(143a-157a)**

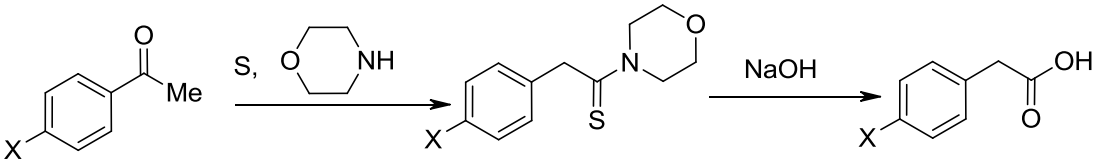
4.1.5.2. Synthesis of 4-chloro-2-substituted *N*-amidinobenzamides **(143b-157b)**

4.1.6. Synthesis of 2-substituted 4-chloro-*N*-pyridin-2-ylbenzamide derivatives (159-173)

4.1.1. Synthesis of 1,2-diaryl-1,2-ethanedione derivatives

4.1.1.1. Synthesis of substituted phenylacetic acids (3, 6, 9, 11)

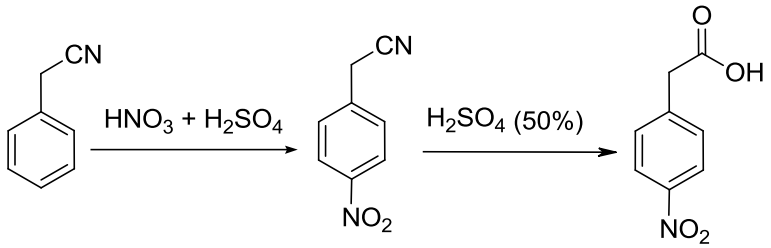
Commercially available 4-chloroacetophenone **(1)** was used for the preparation of 4-chlorophenylacetic acid by the reported procedures through Kindler-modified Willgerodt reaction.[1] 4-Chloroacetophenone **(1)** was refluxed with sulphur in morpholine to afford the thiomorpholide **(2)**. The thiomorpholide without further purification and characterization was hydrolysed in alkaline media to afford the desired 4-chlorophenylacetic acid **(3) (Scheme I)**. It showed a broad peak of -OH at 3325 cm^{-1} and C=O str. at 1705 cm^{-1}. 4-Methylphenylacetic acid **(6)** was also synthesized as per the method for compound **(3)** by replacing 4-chloroaceto-phenone **(1)** with commercially available 4-methylacetophenone **(4)** to afford the desired 4-methylphenylacetic acid **(6)**. It showed a broad peak of -OH at 3011 cm^{-1} and C=O str. at 1691 cm^{-1}.



(1) X = Cl **(2)** X = Cl **(3)** X = Cl
(4) X = Me **(5)** X = Me **(6)** X = Me

Scheme I

4-Nitrophenylacetic acid **(9)** was synthesized by nitration of benzyl cyanide **(7)** in presence of fuming nitric acid followed by hydrolysis of the *p*-nitro product **(8)** under acidic conditions[2] (**Scheme II**). Its IR spectrum showed strong peaks at 1514 (N=O asym. str.), 1345 (N=O sym. str.) and 1707 cm^{-1} (C=O str.).

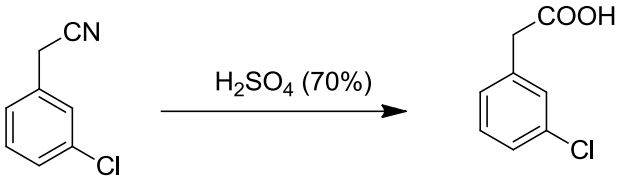


(7) **(8)** **(9)**

Scheme II

3-Chlorophenylacetic acid **(11)** was synthesized by acidic hydrolysis of commercially available 3-chlorobenzyl cyanide **(10)** (**Scheme III**).

It showed a broad peak of -OH at 3010 cm^{-1} and C=O str at 1706 cm^{-1}.



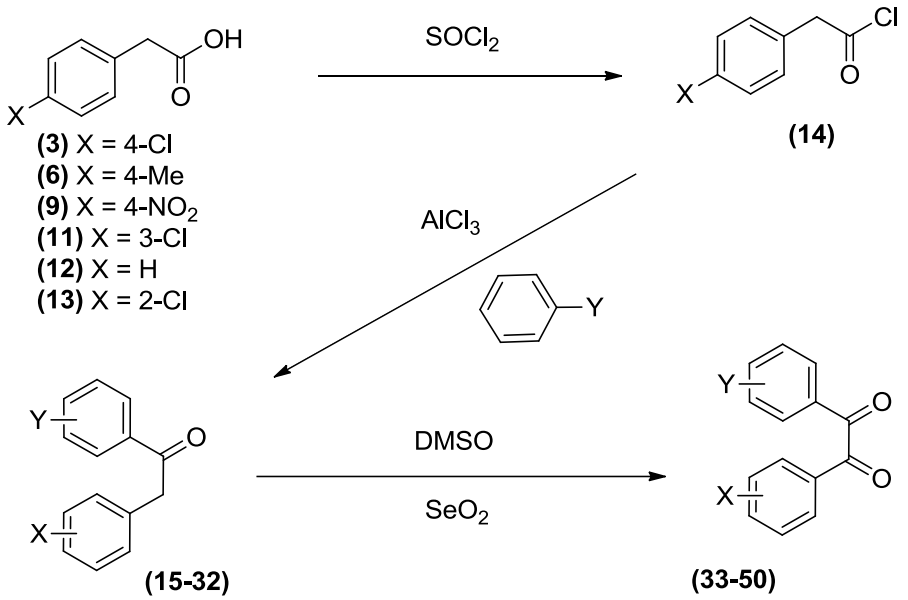
(10) **(11)**

Scheme III

The commercially available phenylacetic acid **(12)** and 2-chlorophenylacetic acid **(13)** were used as such for the next step.

4.1.1.2. Synthesis of substituted diarylethanones (15-32) by Friedel-Craft acylation

Various substituted diarylethanones **(15-32)** were important intermediates required for this work. Acetyl chlorides were prepared by treating the corresponding phenylacetic acids with thionyl chloride. Friedel-Craft acylation reaction[3] was carried out using dry $AlCl_3$, the respective phenylacetyl chlorides **(14)** and substituted benzenes to obtain the substituted diarylethanones or deoxybenzoins **(15-32)**, as common intermediates. The synthesis was carried out following **Scheme IV**. The derivatives were characterized on the basis of their IR spectra which showed shifting of characteristic peak of C=O from 1705 to 1670 cm^{-1} and the disappearance of peak of carboxylic -OH at around 3300 cm^{-1}.



Comp.	X	Y	Comp.	X	Y
(15, 33)	H	4-Me	**(24, 42)**	4-Cl	H
(16, 34)	H	4-Br	**(25, 43)**	4-Cl	4-SMe
(17, 35)	H	4-OMe	**(26, 44)**	4-NO_2	4-Me
(18, 36)	H	4-F	**(27, 45)**	4-NO_2	H
(19, 37)	H	4-SMe	**(28, 46)**	4-Me	4-Me
(20, 38)	4-Cl	4-Me	**(29, 47)**	2-Cl	4-Cl
(21, 39)	4-Cl	4-Br	**(30, 48)**	2-Cl	4-SMe
(22, 40)	4-Cl	4-F	**(31, 49)**	3-Cl	4-Me
(23, 41)	4-Cl	4-Cl	**(32, 50)**	H	H

Scheme- IV

4.1.1.3. Oxidation of substituted diarylethanones to obtain diketo compounds (33-50)

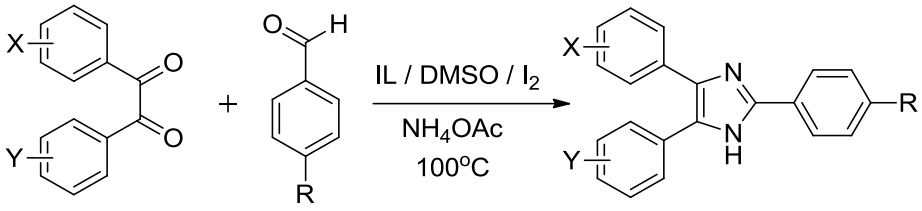
The common intermediates **(15-32)** were oxidised by reacting them with selenium dioxide (SeO_2) in DMSO medium to obtain the dione derivatives **(33-50) (Scheme IV)**. The corresponding 1-(4-substituted phenyl)-2-(substituted phenyl)ethanediones **(33-50)** were synthesized by microwave irradiation of the mixture of DMSO and equivalent quantities of selenium dioxideand substituted diarylethanones **(15-32)**. Generally, this reaction has been carried out in glacial acetic acid and selenium dioxide by conventional heating for a prolonged time.[4] Unlike conventional methods, microwave assisted selenium dioxide oxidation of ethanone derivatives using DMSO as solvent simplifies the workup procedure and noteworthy reduction in the reaction time.[5] The pure compounds were obtained by recrystallisation of the crude products in methanol, as shiny yellow, white or greenish needle shaped crystals.Some ethanedione derivatives obtained as oily or sticky materials were used in the next step without purification. All of the synthesized derivatives **(33-50)** were characterized on the basis of their IR spectra. The purity of the derivatives was checked by TLC in different solvent systems.

4.1.2. Synthesis of 2-substituted 4,5-diaryl-1*H*-imidazole derivatives

4.1.2.1. Synthesis of 2-(4-chlorophenyl)-4,5-diaryl-1*H*-imidazoles (52a-68a)

Synthesis of 2-(4-chlorophenyl)-4,5-diaryl-1*H*-imidazoles (**52a-68a**) was accomplished by the general **Scheme V**. As per the literature reports[6] 4,5-diaryl-1*H*-imidazoles are obtained by reacting a diketone with benzaldehyde. The intermediates (**33-50**), ammonium acetate and 4-

chlorobenzaldehyde were refluxed for 8-12 hr in glacial acetic acid to obtain the corresponding substituted 2-(4-chlorophenyl)-4,5-diaryl-1*H*-imidazoles.



(33-50) **(51a)** R = 4-Cl **(51b)** R = 4-F **(52a-68a)** R = 4-Cl **(52b-68b)** R = 4-F

Comp.	X	Y	Comp.	X	Y
(52)	H	4-Me	**(61)**	4-Cl	H
(53)	H	4-Br	**(62)**	4-Cl	4-SMe
(54)	H	4-OMe	**(63)**	4-NO_2	4-Me
(55)	H	4-F	**(64)**	4-NO_2	H
(56)	H	4-SMe	**(65)**	4-Me	4-Me
(57)	4-Cl	4-Me	**(66)**	2-Cl	4-Cl
(58)	4-Cl	4-Br	**(67)**	2-Cl	4-SMe
(59)	4-Cl	4-F	**(68)**	3-Cl	4-Me
(60)	4-Cl	4-Cl			

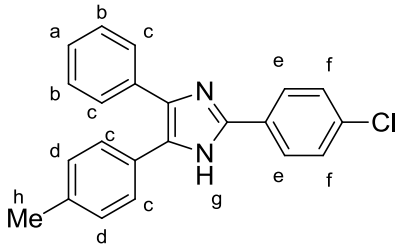
Scheme-V

The observed reaction time was much longer and the yields were low to moderate. As we were interested in green chemical techniques to synthesize a variety of heterocyclic molecules, we used a mixture of ionic liquid $(BbIm)^+Br^-$ in DMSO (1:10) for this synthesis. Interestingly, the reaction did not proceed beyond 50 % on the basis of isolated yields, with relatively longer reaction time. Considering the low acidity of $(BbIm)^+Br^-$, we tried another ionic liquid $(HbIm)^+BF_4^-$ for the samereaction at 110 ^oC. To our surprise, the reaction got completed within only 30 min. Again the catalytic addition of moleculer iodine resulted in noteworthy decrease in the reaction time and increase in yield. The quantity of ammonium acetate was optimized as 4 equivalents which was found to be giving the best results. So, one pot synthesis of all 4,5-diaryl-1*H*-imidazoles was achieved in the said mixture in much lesser time (5-20 min) than the conventional method. The work up of the reaction mixture was also simple as quenching of the reaction mixture with ice and filtration of the precipitates only were required. All the compounds

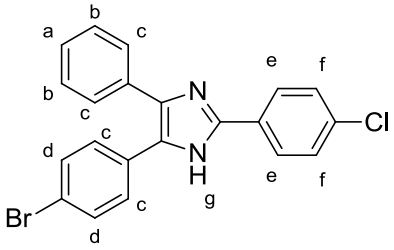
were recrystallized in methanol after decolouration with charcoal. Purity of all of the synthesized compounds was checked by TLC in different solvent systems. All of the synthesized derivatives were characterized by their IR, ^{1}H NMR, elemental analysis and mass spectra.

1-Phenyl-2-*p*-tolylethane-1,2-dione **(33)** was reacted with 4-chlorobenzaldehyde **(51a)** in presence of ammonium acetate to yield 2-(4-chlorophenyl)-4-phenyl-5-*p*-tolyl-1*H*-imidazole **(52a)** as white crystals. IR spectrum of compound **(52a)** displayed the characteristic peaks at 3389 (N-H str.) and 1257 (C-N str.). It offered signals at δ 2.34 (*s*, 3H, ArCH_{3h}), 7.15-7.17 (*d*, 2H, ArH_d), 7.24-7.28 (*m*, 1H, ArH_a), 7.31-7.35 (*m*, 2H, ArH_b), 7.40-7.47 (*m*, 4H, ArH_c), 7.52-7.54 (*d*, 2H, ArH_e), 8.08-8.11 (*d*, 2H, ArH_f) and 12.64 (*bs*, 1H, NH_g) in its ^{1}H NMR spectrum.

Similarly, 1-(4-bromophenyl)-2-phenylethane-1,2-dione **(34)** was reacted with 4-chloro-benzaldehyde **(51a)** to yield 5-(4-bromophenyl)-2-(4-chlorophenyl)-4-phenyl-1*H*-imidazole **(53a)**. Its IR spectrum showed characteristic peaks at 3449 (N-H str.) and 1295 (C-N str.). It offered signals at δ 7.09-7.11 (*m*, 1H, ArH_a), 7.24-7.26 (*m*, 2H, ArH_b), 7.39-7.41 (*d*, 2H, ArH_d), 7.57-7.60 (*d*, 2H, ArH_e), 7.83-7.84 (*d*, 2H, ArH_f) and 7.87-7.92 (*m*, 4H, ArH_c) in its ^{1}H NMR spectrum. The N-H proton was not observed in its spectrum. Its mass spectrum displayed peaks at m/z 408.26 and m/z 410.65.



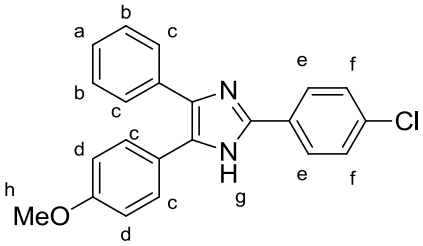
(52a)



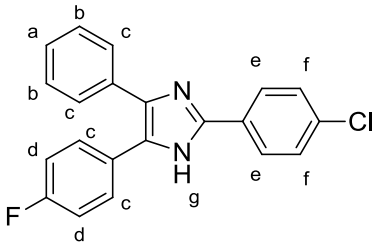
(53a)

2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-4-phenyl-1*H*-imidazole **(54a)** was prepared by the reaction between 1-(4-methoxyphenyl)-2-phenylethane-1,2-dione **(35)** and 4-chloro-benzaldehyde **(51a)**. Its IR spectrum showed characteristic peaks at 3280 (N-H str.) and 1250 (C-N str.). It showed signals at δ 3.81 (*s*, 3H, OCH_{3h}), 6.99-7.01 (*d*, 2H, ArH_d), 7.18-7.22 (*m*, 1H, ArH_a), 7.27-7.29 (*m*, 2H, ArH_b), 7.40-7.51 (*m*, 4H, ArH_c), 7.54-7.56 (*d*, 2H, ArH_e), 8.07-8.09 (*d*, 2H, ArH_f) and 12.64 (*s*, 1H, NH_g) in its ^{1}H NMR spectrum.

2-(4-Chlorophenyl)-5-(4-fluorophenyl)-4-phenyl-1*H*-imidazole **(55a)** was also prepared in similar manner from 1-(4-fluorophenyl)-2-phenylethane-1,2-dione **(36)** which showed 3257 (N-H str) and 1225 (C-N str) cm^{-1} peaks in its IR spectrum. It displayed signals at δ 6.96-7.00 (*m*, 2H, ArH_b), 7.26-7.37 (*m*, 5H, ArH_a and ArH_c), 7.43-7.47 (*m*, 4H, ArH_d and ArH_e) and 7.85-7.87 (*d*, 2H, ArH_f) in its ^{1}H NMR spectrum. The N-H proton was not observed in its spectrum. Its mass spectrum displayed M+1 peak at m/z 348.06 and M+2 peak at m/z 349.67.



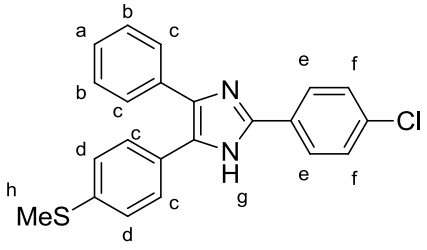
(54a)



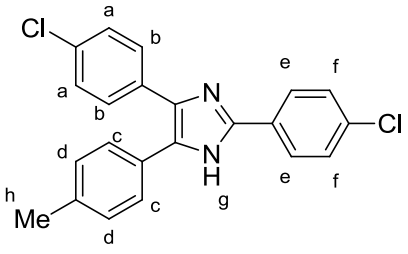
(55a)

The reaction between 1-(4-methylthiophenyl)-2-phenylethane-1,2-dione **(37)** and 4-chlorobenzaldehyde **(51a)** resulted into 2-(4-chlorophenyl)-5-(4-methylthiophenyl)-4-phenyl-1*H*-imidazole **(56a)** as the final product. In its IR spectrum peaks at 3412 (N-H str.) and 1320 (C-N str.) cm^{-1} were observed. It offered signals at δ 2.49 (*s*, 3H, SCH_{3h}), 7.21-7.23 (*d*, 2H, ArH_d), 7.29-7.30 (*m*, 1H, ArH_a), 7.35-7.37 (*m*, 2H, ArH_b), 7.45-7.48 (*m*, 4H, ArH_c), 7.52-7.54 (*d*, 2H, ArH_e), 8.08-8.10 (*d*, 2H, ArH_f) and 12.75 (*bs*, 1H, NH_g) in its ^{1}H NMR spectrum.

2,4-Bis(4-chlorophenyl)-5-*p*-tolyl-1*H*-imidazole **(57a)** was prepared from 1-(4-chlorophenyl)-2-*p*-tolylethane-1,2-dione **(38)** showing peaks at 3412 (N-H str.) and 1251 (C-N str.) cm^{-1} in its IR spectrum. The ^{1}H NMR spectrum of this compound showed signals at δ 2.37 (*s*, 3H, ArCH_{3h}), 7.21-7.23 (*d*, 2H, ArH_d), 7.33-7.35 (*d*, 2H, ArH_a), 7.41-7.43 (*d*, 2H, ArH_c), 7.47-7.49 (*d*, 2H, ArH_b), 7.55-7.57 (*d*, 2H, ArH_e) and 7.97-7.99 (*d*, 2H, ArH_f). The N-H proton was not observed in its spectrum.

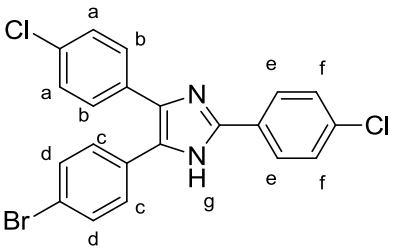


(56a)

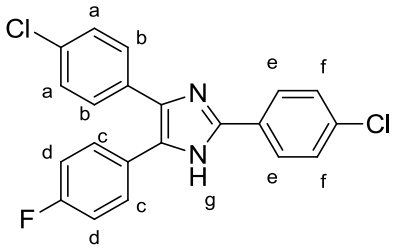


(57a)

Compound 5-(4-bromophenyl)-2,4-bis(4-chlorophenyl)-1*H*-imidazole **(58a)** has been prepared by reacting 1-(4-bromophenyl)-2-(4-chlorophenyl)ethane-1,2-dione **(39)** with 4-chlorobenzaldehyde **(51a)** in the same medium. It showed characteristic peaks at 3447 (N-H str.) and 1318 (C-N str.) cm^{-1} and absence of carbonyl stretching in its IR spectrum.^{1}H NMR spectrumobtained from its crystalsshowed signals at δ 7.38-7.40 (*d*, 2H, ArH_d), 7.45-7.55 (*m*, 8H, ArH_a, ArH_b, ArH_c and ArH_e) and 8.14-8.16 (*d*, 2H, ArH_f). The N-H proton was not observed in its spectrum. Mass spectrum of compound **(58a)** showed molecular ion (M^+) peak at m/z 442.23 along with M+2 at m/z 444.22 and M+4 at m/z 446.12.



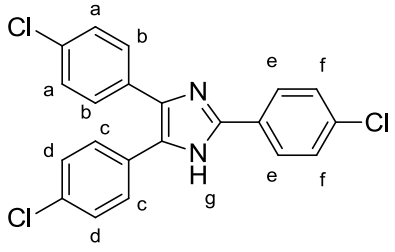
(58a)



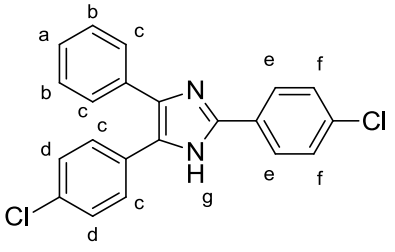
(59a)

Similarly, 2,4-bis(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole **(59a)** was synthesized by the reaction between 1-(4-chlorophenyl)-2-(4-fluorophenyl)ethane-1,2-dione **(40)** and 4-chlorobenzaldehyde. Its IR spectrum showed characteristic peaks at 3423 (N-H str.) and 1255 (C-N str.) cm^{-1}. In its ^{1}H NMR spectrum, it showed signals at δ 7.14-7.18 (*m*, 2H, ArH_d), 7.35-7.37 (*m*, 2H, ArH_a), 7.46-7.55 (*m*, 6H, ArH_b, ArH_c and ArH_e), 8.08-8.10 (*d*, 2H, ArH_f) and 13.02 (*bs*, 1H, NH_g).

2,4,5-*Tris*(4-chlorophenyl)-1*H*-imidazole **(60a)** was obtained from 1,2-bis(4-chlorophenyl)ethane-1,2-dione **(41)**. Its IR spectrum showed characteristic peaks at 3448 (N-H str.) and 1259 (C-N str.) cm^{-1}. It offered signals at δ 7.36-7.38 (*d*, 4H, ArH_a & ArH_d), 7.46-7.48 (*d*, 2H, ArH_e), 7.51-7.53 (*d*, 4H, ArH_b & ArH_c) and 8.12-8.14 (*d*, 2H, ArH_f) in its ^{1}H NMR spectrum. The N-H proton was not observed in its spectrum.



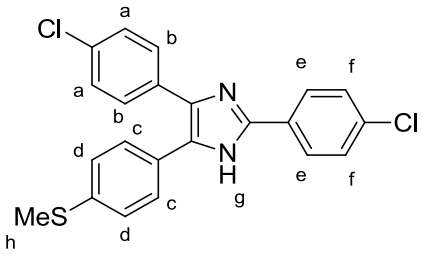
(60a)



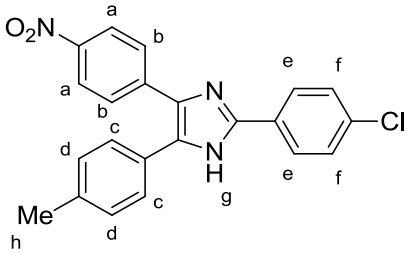
(61a)

In a similar way, 1-(4-chlorophenyl)-2-phenylethane-1,2-dione **(42)** was converted into 2,5-bis(4-chlorophenyl)-4-phenyl-1*H*-imidazole **(61a)** which showed peaks at 3382 (N-H str.) and 1253 (C-N str.) cm^{-1} in IR spectrum. It displayed signals at δ 7.28-7.34 (*m*, 3H, ArH_a and ArH_d), 7.36-7.43 (*m*, 4H, ArH_c), 7.52-7.55 (*m*, 4H, ArH_b and ArH_e), 8.08-8.11 (*d*, 2H, ArH_f) and 12.68 (*bs*, 1H, NH_g) in its ^{1}H NMR spectrum.

2,4-Bis(4-chlorophenyl)-5-(4-methylthiophenyl)-1*H*-imidazole **(62a)** was obtained from 1-(4-chlorophenyl)-2-(4-methylthiophenyl)ethane-1,2-dione **(43)**. Its IR spectrum showed characteristic peaks at 3411 (N-H str.) and 1276 (C-N str.) cm^{-1}. It offered signals at δ 2.49 (s, 3H, SCH_{3h}), 7.24-7.26 (*d*, 2H, ArH_a), 7.33-7.36 (*m*, 2H, ArH_d), 7.44-7.47 (*m*, 4H, ArH_b and ArH_c), 7.53-7.55 (*d*, 2H, ArH_e), 8.07-8.09 (*d*, 2H, ArH_f) and 12.75 (*bs*, 1H, NH_g) in its ^{1}H NMR spectrum.



(62a)



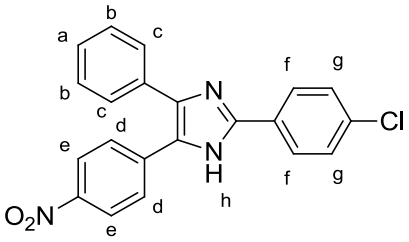
(63a)

In a similar way, 1-(4-nitrophenyl)-2-*p*-tolylethane-1,2-dione **(44)** was converted into 2-(4-chlorophenyl)-4-(4-nitrophenyl)-5-*p*-tolyl-1*H*-imidazole **(63a)** showing peaks at 3339 (N-H str.), 1256 (C-N str.), 1506 and 1327 (NO_2) cm^{-1} in its IR spectrum. It displayed signals at δ 2.40 (*s*, 3H, ArCH_{3h}), 7.26-7.28 (*d*, 2H, ArH_d), 7.41-7.43 (*d*, 2H, ArH_c), 7.46-7.49 (*d*, 2H, ArH_e), 7.80-7.82 (*d*, 2H, ArH_b), 8.10-8.14 (*dd*, 4H, ArH_a and ArH_f) and 12.98 (*bs*, 1H, NH_g) in its ^{1}H NMR spectrum.

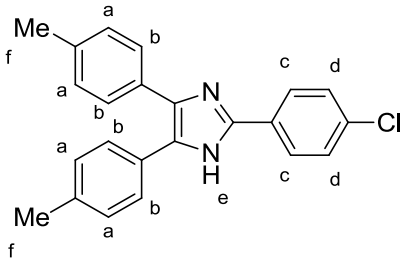
2-(4-Chlorophenyl)-5-(4-nitrophenyl)-4-phenyl-1*H*-imidazole **(64a)** was synthesized from 1-(4-nitrophenyl)-2-phenylethane-1,2-dione **(45)**. Its IR spectrum showed characteristic peaks at 3351 (N-H str.), 1506 and 1328 (NO_2), and 1258 (C-N str.) cm^{-1}. It offered signals at δ 7.45-7.51 (*m*, 5H, ArH_a, ArH_b, ArH_c), 7.53-7.55 (*d*, 2H, ArH_d), 7.79-7.81 (*d*, 2H, ArH_f), 8.11-8.16 (*dd*, 4H, ArH_e and ArH_g) and 12.98 (*bs*, 1H, NH_h) in its ^{1}H NMR spectrum.

In a similar way, 1,2-di-*p*-tolylethane-1,2-dione **(46)** was converted into 2-(4-chlorophenyl)-4,5-di-*p*-tolyl-1*H*-imidazole **(65a)** which showed peaks at 3413 (N-H str.) and

1253 (C-N str.) cm^{-1} in its IR spectrum. It displayed signals at δ 2.33 (*s*, 6H, ArCH_{3f}), 7.14-7.15 (*dd*, 4H, ArH_a), 7.40-7.42 (*dd*, 4H, ArH_b), 7.44-7.47 (*d*, 2H, ArH_c), 8.07-8.09 (*d*, 4H, ArH_d) and 12.56 (*bs*, 1H, NH_e) in its ^{1}H NMR spectrum.



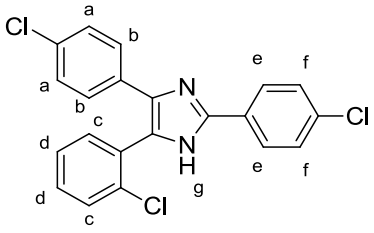
(64a)



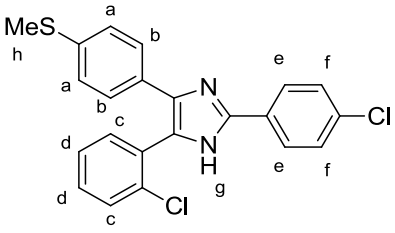
(65a)

5-(2-Chlorophenyl)-2,4-bis(4-chlorophenyl)-1*H*-imidazole **(66a)** was afforded from 1-(2-chlorophenyl)-2-(4-chlorophenyl)ethane-1,2-dione **(47)**. Its IR spectrum showed characteristic peaks at 3421 (N-H str.) and 1259 (C-N str.) cm^{-1}. It offered signals at δ 7.26-7.28 (*d*, 2H, ArH_b), 7.44-7.53 (*m*, 7H, ArH_a, ArH_c, ArH_d & ArH_f), 7.58 (*d*, 1H, ArH_c), 8.07-8.09 (*d*, 2H, ArH_e) and 12.94 (*bs*, 1H, NH_g) in its ^{1}H NMR spectrum.

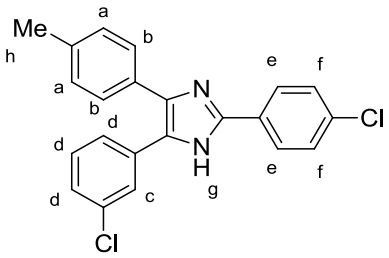
In a similar way, 1-(2-chlorophenyl)-2-(4-methylthiophenyl)ethane-1,2-dione **(48)** was converted into 5-(2-chlorophenyl)-2-(4-chlorophenyl)-4-(4-methylthiophenyl)-1*H*-imidazole **(67a)** which showed peaks at 3422 (N-H str.) and 1260 (C-N str.) cm^{-1} in its IR spectrum. It displayed signals at δ 2.44 (*s*, 3H, SCH_{3h}), 7.12-7.14 (*d*, 2H, ArH_a), 7.33-7.36 (*d*, 2H, ArH_b), 7.42-7.55 (*m*, 6H, ArH_c, ArH_d and ArH_f), 8.07-8.09 (*d*, 2H, ArH_e) and 12.79 (*bs*, 1H, NH_g) in its ^{1}H NMR spectrum.



(66a)



(67a)



(68a)

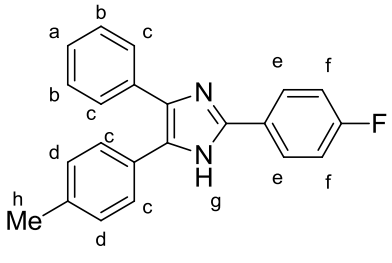
5-(3-Chlorophenyl)-2-(4-chlorophenyl)-4-*p*-tolyl-1*H*-imidazole **(68a)** was obtained from 1-(3-chlorophenyl)-2-(4-methylphenyl)ethane-1,2-dione **(49)**. Its IR spectrum showed peaks at 3424 (N-H str.) and 1247 (C-N str.) cm^{-1}. It offered signals at δ 2.37 (*s*, 3H, ArCH_{3h}), 7.20-7.24

(*m*, 4H, ArH_a and ArH_b), 7.41-7.45 (*m*, 5H, ArH_d and ArH_f), 7.63 (*s*, 1H, ArH_c), 8.09-8.11 (*d*, 2H, ArH_e) and 12.87 (*bs*, 1H, NH_g) in its ^{1}H NMR spectrum.

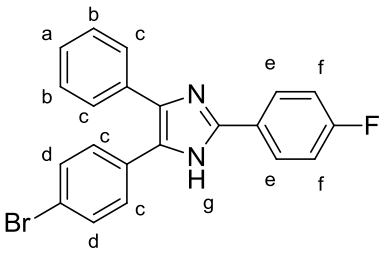
4.1.2.2. Synthesis of 2-(4-fluorophenyl)-4,5-diaryl-1*H*-imidazoles (52b-68b)

Synthesis of 2-(4-fluorophenyl)-4,5-diaryl-1*H*-imidazoles (**52b-68b**) was accomplished as per the general **Scheme V**. As described earlier, the intermediates (**33-50**), ammonium acetate and 4-fluorobenzaldehyde **(51b)** were reacted in a mixture of ionic liquid $(HbIm)^+BF_4^-$ and DMSO in a fixed ratio of 1:10 at 110 ^oC. The one pot syntheses of all 2-(4-fluorophenyl)-4,5-diaryl-1*H*-imidazoles were carried out in the above-mentioned mixture in short reaction times (7-18 min) in higher yields. The reaction mixture was simply quenched with crushed ice and the precipitated solid was filtered off to get the desired products. All the compounds were treated with activated charcoal and recrystallized in methanol. Purity of all of the synthesized compounds was checked by TLC in different solvent systems. All of the synthesized derivatives were characterized by their IR, ^{1}H NMR, elemental analysis and mass spectra.

1-Phenyl-2-*p*-tolylethane-1,2-dione **(33)** was reacted with 4-fluorobenzaldehyde **(51b)** in the presence of ammonium acetate to yield 2-(4-fluorophenyl)-4-phenyl-5-*p*-tolyl-1*H*-imidazole **(52b)** as white crystals. IR spectrum of compound **(52b)** displayed the characteristic peaks at 3341 (N-H str.) and 1226 (C-N str.) cm^{-1}. In its ^{1}H NMR spectrum, it showed signals at 2.38 (*s*, 3H, ArCH_{3h}), 7.00-7.72 (*m*, 11H, ArH_a, ArH_b, ArH_c, ArH_d and ArH_e), 8.10-8.14 (*dd*, 2H, ArH_f) and 12.47 (*bs*, 1H, NH_g). Its mass spectrum displayed M+1 peak at m/z 328.42. All 4-(4-substituted phenyl)-2-(4-fluorophenyl)-5-substituted phenyl-1*H*-imidazoles **(52b-68b)** were prepared in a similar way from the intermediates **(33-49)**. All of the synthesized derivatives **(52b-68b)** showed characteristic peaks at 3432-3454 (N-H str.) and 1200-1240 (C=N str.) cm^{-1} in their IR spectra.



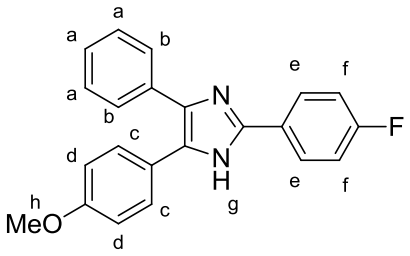
(52b)



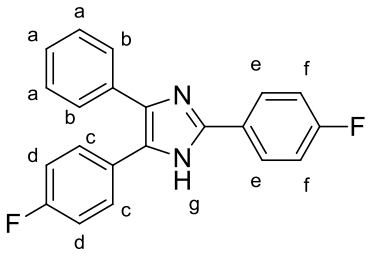
(53b)

Similarly, 1-(4-bromophenyl)-2-phenylethane-1,2-dione **(34)** was reacted with 4-fluoro-benzaldehyde **(51b)** to yield 5-(4-bromophenyl)-2-(4-fluorophenyl)-4-phenyl-1*H*-imidazole **(53b)**. Its IR spectrum showed characteristic peaks at 3322 (N-H str.) and 1229 (C-N str.) cm^{-1}. It displayed signals at δ 7.17-7.21 (*m*, 2H, ArH_b), 7.32-7.38 (*m*, 3H, ArH_a & ArH_e), 7.46-7.53 (*m*, 6H, ArH_c & ArH_d), 8.09-8.14 (*dd*, 2H, ArH_f) and 12.68 (*bs*, 1H, NH_g) in its ^{1}H NMR spectrum.

2-(4-Fluorophenyl)-5-(4-methoxyphenyl)-4-phenyl-1*H*-imidazole **(54b)** was prepared by the reaction between the 1-(4-methoxyphenyl)-2-phenylethane-1,2-dione **(35)** and 4-fluoro-benzaldehyde **(51b)**. Its IR spectrum showed characteristic peaks at 3412 (N-H str.) and 1245 (C-N str.) cm^{-1}. It displayed signals at δ 3.80(*s*, 3H, OCH_{3h}), 6.90-6.92 (*d*, 2H, ArH_d), 7.18-7.26 (*m*, 3H, ArH_a), 7.31-7.34 (*dd*, 2H, ArH_c), 7.43-7.46 (*d*, 2H, ArH_e), 7.53-7.55 (*d*, 2H, ArH_b), 8.09-8.13 (*dd*, 2H, ArH_f) and 12.61 (*bs*, 1H, NH_g) ppm in its ^{1}H NMR spectrum.



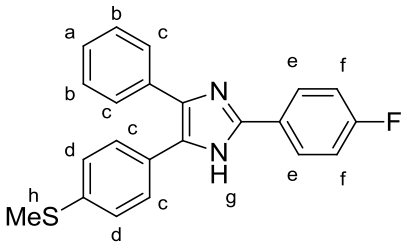
(54b)



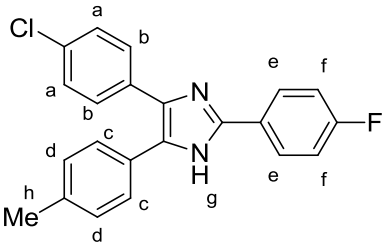
(55b)

2,5-Bis(4-Fluorophenyl)-4-phenyl-1*H*-imidazole **(55b)** was prepared by the reaction between 1-(4-fluorophenyl)-2-phenylethane-1,2-dione **(36)** and 4-fluorobenzaldehyde **(51b)**. Its IR spectrum showed characteristic peaks at 3410 (N-H str.) and 1226 (C-N str.) cm^{-1}. It displayed ^{1}H NMR signals at δ 6.78-7.66 (*m*, 13H, ArH_a, ArH_b, ArH_c, ArH_d, ArH_e and ArH_f) and 12.51 (*bs*, 1H, NH_g). Its mass spectrum showed the M+1 peak at m/z 328.28.

2-(4-Fluorophenyl)-5-(4-methylthiophenyl)-4-phenyl-1*H*-imidazole **(56b)** was obtained from reaction between 1-(4-methylthiophenyl)-2-phenylethane-1,2-dione **(37)** and 4-flurobenz-aldehyde **(51b)**. Its IR spectrum showed characteristic peaks at 3380 (N-H str.) and 1228 (C-N str.) cm^{-1}. It displayed ^{1}H NMR signals at δ 2.50 (*s*, 3H, SCH_{3h}), 7.20-7.34 (*m*, 9H, ArH_a, ArH_b, ArH_c & ArH_d), 7.45-7.51 (*m*, 4H, ArH_e and ArH_f) and 12.76 (*bs*, 1H, NH_g).



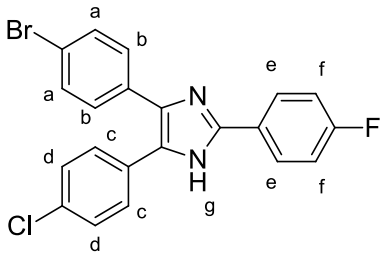
(56b)



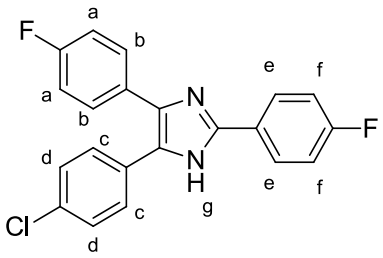
(57b)

Similarly, 4-(4-chlorophenyl)-2-(4-fluorophenyl)-5-*p*-tolyl-1*H*-imidazole **(57b)** was prepared from 1-(4-chlorophenyl)-2-*p*-tolylethane-1,2-dione **(38)** which showed 3420 (N-H str.) and 1230 (C-N str.) cm^{-1} in its IR spectrum and displayed signals at δ 2.37 (*s*, 3H, ArCH_{3h}), 7.15-7.20 (*m*, 4H, ArH_b & ArH_c), 7.28-7.30 (*d*, 2H, ArH_d), 7.39-7.41 (*d*, 2H, ArH_e), 7.53-7.55 (*d*, 2H, ArH_a), 8.09-8.13 (*dd*, 2H, ArH_f) and 12.61 (*bs*, 1H, NH_g) ppm in its ^{1}H NMR spectrum.

4-(4-Bromophenyl)-5-(4-chlorophenyl)-2-(4-fluorophenyl)-1*H*-imidazole **(58b)** was obtained fromthe reaction between 1-(4-methylthiophenyl)-2-phenylethane-1,2-dione **(39)** and 4-flurobenzaldehyde **(51b)**. Its IR spectrum showed characteristic peaks at 3418 (N-H str) and 1230 (C-N str) cm^{-1}.It displayed ^{1}H NMR signals at δ 7.01-8.12 (*m*, 12H, ArH_a, ArH_b, ArH_c, ArH_d, ArH_e & ArH_f) and 12.60 (*bs*, 1H, NH_g) ppm.



(58b)

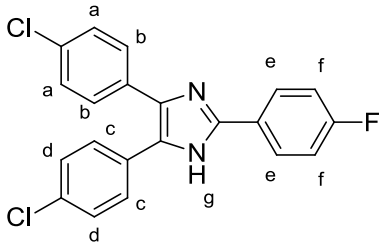


(59b)

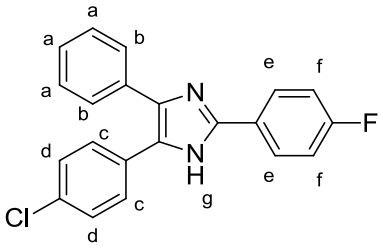
Similarly, 5-(4-chlorophenyl)-2,4-bis(4-fluorophenyl)-1*H*-imidazole **(59b)** was prepared from 1-(4-chlorophenyl)-2-(4-fluorophenyl)ethane-1,2-dione **(40)** which showed 3323 (N-H str.) and 1228 (C-N str.) cm^{-1} in its IR spectrum and displayed ^{1}H NMR signals at δ 7.01-7.07 (*m*, 1H, ArH_d), 7.16-7.20 (*m*, 3H, ArH_c and ArH_d), 7.26-7.28 (*d*, 1H, ArH_a), 7.34-7.44 (*m*, 1H, ArH_a), 7.47-7.57 (*m*, 4H, ArH_b and ArH_e), 8.09-8.12 (*dd*, 2H, ArH_f) and 12.61 (*bs*, 1H, NH_g) ppm.

4,5-Bis(4-chlorophenyl)-2-(4-fluorophenyl)-1*H*-imidazole **(60b)** was obtained from the reaction between 1,2-bis(4-chlorophenyl)ethane-1,2-dione **(41)** and 4-flurobenzaldehyde **(51b)**.

Its IR spectrum showed characteristic peaks at 3419 (N-H str.) and 1232 (C-N str.) cm^{-1}. It displayed ^1H NMR signals at δ 7.17-7.21 (*dd*, 2H, ArH_c), 7.28-7.30 (*d*, 2H, ArH_b), 7.41-7.43 (*d*, 2H, ArH_a), 7.48-7.50 (*d*, 2H, ArH_d), 7.54-7.56 (*d*, 2H, ArH_e), 8.09-8.13 (*dd*, 2H, ArH_f) and 12.63 (*bs*, 1H, NH_g).



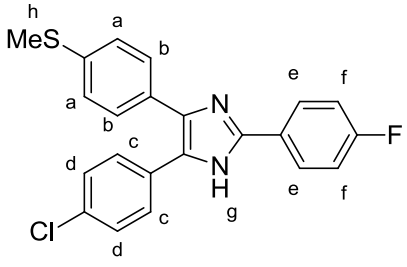
(60b)



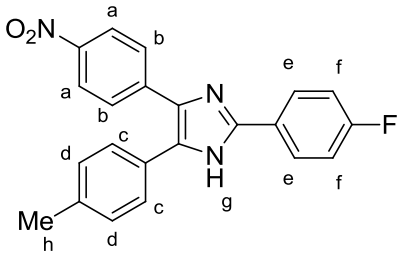
(61b)

Similarly, 5-(4-chlorophenyl)-2-(4-fluorophenyl)-4-phenyl-1*H*-imidazole **(61b)** was obtained from 1-(4-chlorophenyl)-2-phenylethane-1,2-dione **(42)** which showed 3340 (N-H str.) and 1227 (C-N str.) cm^{-1} in its IR spectrum and displayed signals at δ 7.15-7.20 (*dd*, 2H, ArH_b), 7.29-7.31 (*m*, 3H, ArH_a), 7.36-7.44 (*d*, 2H, ArH_c), 7.51-7.55 (*dd*, 4H, ArH_d and ArH_e), 8.08-8.14 (*dd*, 2H, ArH_f) and 12.58 (*bs*, 1H, NH_g) ppm in its ^1H NMR spectrum.

In the similar fashion, 5-(4-chlorophenyl)-2-(4-fluorophenyl)-4-(4-methylthiophenyl)-1*H*-imidazole **(62b)** and 2-(4-fluorophenyl)-4-(4-nitrophenyl)-5-*p*-tolyl-1*H*-imidazole **(63b)** both were prepared from 1-(4-chlorophenyl)-2-(4-methylthiophenyl)ethane-1,2-dione **(43)** and 1-(4-nitrophenyl)-2-*p*-tolylethane-1,2-dione **(44)** repectively. Both of them showed peaks at 3410 (N-H str.), 1231 (C-N str.), and 3376 (N-H str.), 1509, 1335 (NO_2) and 1229 (C-N str.) cm^{-1} in their



(62b)

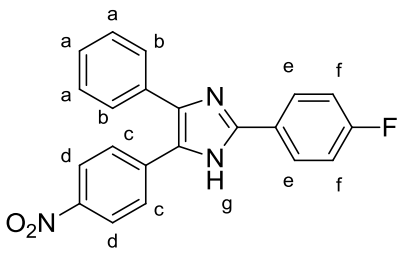


(63b)

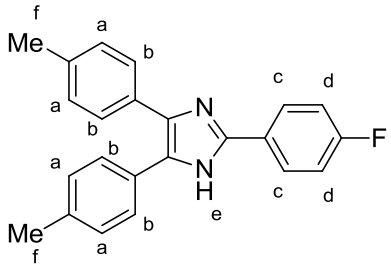
respective IR spectra. The former compound **(62b)** showed signals at δ 2.48 (*s*, 3H, SCH_{3h}), 7.06-7.10 (*dd*, 2H, ArH_c), 7.17-7.19 (*d*, 2H, ArH_d), 7.25-7.27 (*dd*, 2H, ArH_b), 7.32-7.36 (*d*, 2H, ArH_e), 7.42-7.44 (*d*, 2H, ArH_f) and 7.82-7.85 (*dd*, 2H, ArH_f) ppm in its ^1H NMR spectrum. The

N-H proton was not observed in its spectrum. The later compound **(63b)** showed ^{1}H NMR signals at δ 2.41 (*s*, 3H, ArCH_{3h}), 7.20-7.30 (*m*, 4H, ArH_a and ArH_d), 7.41-7.44 (*dd*, 2H, ArH_b), 7.81-7.83 (*d*, 2H, ArH_c), 8.12-8.15 (*m*, 4H, ArH_e and ArH_f) and 12.83 (*bs*, 1H, NH_g) ppm.

1-(4-Nitrophenyl)-2-phenylethane-1,2-dione (**45**) was reacted with 4-flurobenzaldehyde **(51b)** to yield 2-(4-fluorophenyl)-5-(4-nitrophenyl)-4-phenyl-1*H*-imidazole **(64b)** which showed characteristic peaks at 3353 (N-H str.), 1551, 1329 (NO_2) and 1226 (C-N str.) cm^{-1} in its IR spectrum. Its ^{1}H NMR showed distinct peaks at δ 7.23-7.27 (*dd*, 2H, ArH_c), 7.43-7.55 (*m*, 5H, ArH_a and ArH_b), 7.81-7.83 (*d*, 2H, ArH_e), 8.11-8.24 (*m*, 4H, ArH_d and ArH_f) and 12.91 (*bs*, 1H, ArH_g) ppm.



(64b)



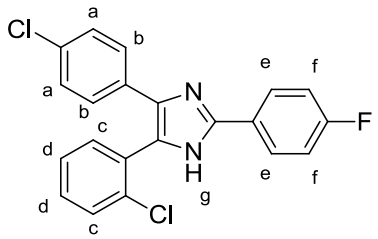
(65b)

On the other side, 2-(4-fluorophenyl)-4,5-di-*p*-tolyl-1*H*-imidazole **(65b)** was prepared from 4-flurobenzaldehyde **(51b)** and 1,2-di-*p*-tolylethane-1,2-dione (**46**) which displayed peaks at 3402 (N-H str.) and 1228 (C-N str.) cm^{-1} in its IR spectrum. Its ^{1}H NMR signals were found at δ 2.30-2.36 (*d*, 6H, ArCH_{3f}), 7.06-7.10 (*m*, 2H, ArH_c), 7.17-7.21 (*m*, 4H, ArH_a), 7.35-7.46 (*m*, 4H, ArH_b), 8.09-8.13 (*m*, 2H, ArH_d) and 12.47 (*bs*, 1H, NH_e) ppm.

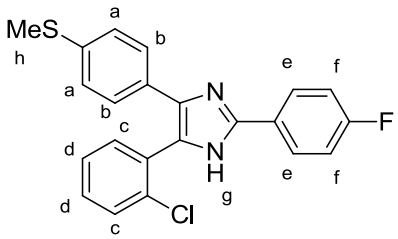
1-(2-Chlorophenyl)-2-(4-chlorophenyl)ethane-1,2-dione (**47**) was reacted with 4-fluro-benzaldehyde **(51b)** to yield 5-(2-chlorophenyl)-4-(4-chlorophenyl)-2-(4-fluorophenyl)-1*H*-imidazole **(66b)** which showed characteristic peaks at 3412 (N-H str.) and 1230 (C-N str.) cm^{-1} in its IR spectrum. Its ^{1}H NMR showed distinct peaks at δ 7.22-7.28 (*m*, 4H, ArH_b and ArH_d), 7.42-7.58 (*m*, 6H, ArH_a, ArH_c and ArH_e), 8.09-8.12 (*dd*, 2H, ArH_f) and 12.83 (*bs*, 1H, NH_g) ppm.

On the similar line, 5-(2-chlorophenyl)-2-(4-fluorophenyl)-4-(4-methylthiophenyl)-1*H*-imidazole **(67b)** was prepared from 4-flurobenzaldehyde **(51b)** and 1-(2-chlorophenyl)-2-(4-methylthiophenyl)ethane-1,2-dione (**48**) which displayed peaks at 3415 (N-H str.) and 1230 (C-N str.) cm^{-1} in its IR spectrum. Its ^{1}H NMR signals were found at δ 2.44 (*s*, 3H, ArCH_{3h}), 7.13

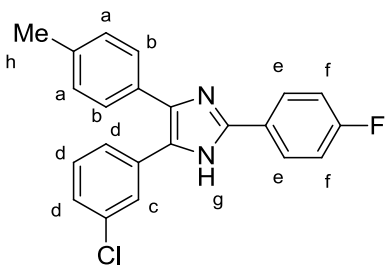
(*m*, 2H, ArH_a), 7.20-7.24 (*m*, 2H, ArH_d), 7.40-7.59 (*m*, 6H, ArH_b, ArH_c & ArH_e), 8.09-8.12 (*dd*, 2H, ArH_f) and 12.73 (*bs*, 1H, NH_h) ppm.



(66b)



(67b)



(68b)

Also, 5-(3-chlorophenyl)-2-(4-fluorophenyl)-4-*p*-tolyl-1*H*-imidazole **(68b)** was prepared from 1-(3-chlorophenyl)-2-*p*-tolylethane-1,2-dione (**49**) and 4-flurobenzaldehyde **(51b)**. In its IR spectrum, characteristic peaks at 3345 (N-H str.) and 1231 (C-N str.) cm^{-1} were observed. Its ^1H NMR showed peaks at δ 2.38 (*s*, 3H, ArCH_{3h}), 7.15-7.27 (*m*, 6H, ArH_a, ArH_b & ArH_e), 7.41-7.42 (*m*, 3H, ArH_d), 7.64 (*s*, 1H, ArH_c), 8.10-8.14 (*dd*, 2H, ArH_f) and 12.69 (*bs*, 1H, NH_h) ppm. Its mass spectrum showed M^+ and (M+2) at m/z 362.15 and 364.25 respectively.

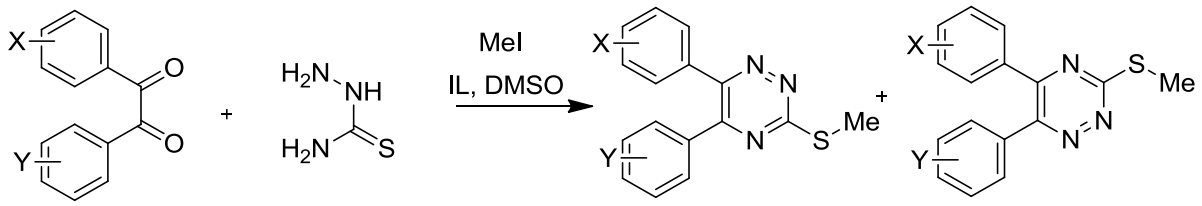
4.1.3. Synthesis of 5,6-diaryl-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine derivatives

4.1.3.1. Synthesis of 5,6-diaryl-3-methylthio-1,2,4-triazines (70-82 and 83-92)

Although many synthetic protocols for 1,2,4-triazines have been reported in the past,[7] there still exists a need for the development of more efficient processes for the synthesis of 1,2,4-triazines. All of the procedures described in the literature have one or more disadvantages, like formation of undesired condensed jelly-like masses as side products, harsh reaction conditions, formation of more than one regioisomers, activation by toxic metals, use of inorganic supports like silica, use of NaOAc or AgOAc, longer reaction times, use of corrosive acids, high temperature or reflux conditions, multistep procedures like preliminary isolation of intermediates like 1,2-diketone-monoacylhydrazones followed by ring closure or use of scarcely available substituted carbazides as starting materials *etc*.

Modifications have been done by substituting solvents and acids/bases as catalysts, but problems like longer reaction times, high temperature conditions and low to moderate reaction yields still persisted. Additionly, almost all of the known methods make use of volatile organic solvents, leading to complex isolation and recovery procedures. Therefore, we sought to develop

a more efficient and convenient method that was flawless and amenable to both laboratory and industrial scale.



(33,36-42,44-46,49,50) **(69)** **(70-82)** **(83-92)**

Comp.	X	Y	Comp.	X	Y
(70)	H	4-Me	**(83)**	4-Me	H
(71)	H	4-F	**(84)**	4-F	H
(72)	H	4-SMe	**(85)**	4-SMe	H
(73)	4-Cl	4-Me	**(86)**	4-Me	4-Cl
(74)	4-Cl	4-Br	**(87)**	4-Br	4-Cl
(75)	4-Cl	4-F	**(88)**	4-F	4-Cl
(76)	4-Cl	4-Cl	-	-	-
(77)	4-Cl	H	**(89)**	H	4-Cl
(78)	4-NO_2	4-Me	**(90)**	4-Me	4-NO_2
(79)	4-NO_2	H	**(91)**	H	4-NO_2
(80)	4-Me	4-Me	-	-	-
(81)	3-Cl	4-Me	**(92)**	4-Me	3-Cl
(82)	H	H	-	-	-

Scheme-VI

Recently, we reported the synthesis of five, six and seven membered cyclic guanidines by the synergy of specific ratio of IL and DMSO at ambient conditions.[8] Hence to utilize this synergistic phenomenon of the above-mentioned mixture, it was envisaged to evaluate its effect on the formation of 5,6-diaryl substituted 1,2,4-triazines from nonsymmetrical diketones and thiosemicarbazide. We extended the investigation of this system toward the synthesis of 1,2,4-triazines by a one-pot condensation of thiosemicarbazide, substituted diketones and methyl iodide to afford the 5,6-diarylsubstituted 3-methylthio-1,2,4-triazines in excellent yields in much shorter reaction times without any added catalyst. In order to determine the optimum conditions for the one pot synthesis of methylthiotriazines, the model reaction of benzil, thiosemicarbazide and methyl iodide was selected. The optimum yields were found with equimolar quantities of benzil and thiosemicarbazide with 1.2 eq. of methyl iodide at 70 ^oC (**Table 1**). When the ratio of

benzil and thiosemicarbazide was changed to 1:1.5, a mixture of sticky polymeric complex was obtained after workup which showed a spot at the base (with low R_f value) in TLC with trace amounts of the desired cyclized product. This is probably because of formation of bishydrazones or dimers which failed further cyclization. For ascertaining the role of solvent for the reaction, different polar aprotic solvents with and without IL were employed in the model reaction as shown in **Table 2**. DMSO gave the best results and hence used for subsequent reactions. DMSO was further investigated as the most desired solvent with different ionic liquids.In each case, the ionic liquid used was in catalytic ratio of 1:10 to that of DMSO.

Table 1: Screening of different mole ratios of reactants

Sr. No.	Mole Ratio[a]	Yield[b] (%)	Time (min)
1	1.0:1.5:1.2	27	21
2	1.0:1.0:1.0	75	17
3	1.0:1.0:1.2	96	15
4	1.0:1.0:0.0	85 (thiol)	25

[a]Mole ratio of benzil:thiosemicarbazide:alkyl halide; [b]Isolated yields

Different ionic liquids, *viz.* 1-butylimidazolium tetrafluoroborate $[HbIm]^+BF_4^-$, 1,3-dibutylimidazolium tetrafluoroborate $[BbIm]^+BF_4^-$, 1-butyl-3-methylimidazoliumbromide $[BmIm]^+Br^-$ and 1-butyl-2,3-dimethylimidazolium tetrafluoroborate $[BmmIm]^+BF_4^-$ were

Table 2: Screening of different solvents with IL $[Bbim]^+Br^-$

Sr. No.	Solvent[a]	Time (min)	Yield[b] (%)
1	DMF	> 1.5 h	42
2	THF	> 5 h	69
3	Acetone	>1.5 h	62
4	Acetonitrile	> 2 h	65
5	DMSO	15 min	90
6	DMSO alone	1 h	75

[a] 1:10 ratio with IL; [b]Isolated yields

evaluated and the results are given in **Table 3**. The ionic liquid $[Bbim]^+Br^-$ in DMSO gave the best results. To justify these results and to scour down the possibility of catalysis of ionic liquid or DMSO alone; the reaction was performed in pure IL without DMSO and separately in DMSO alone. Longer reaction times and moderate yields were observed in both of these cases.

It is interesting to note that when the reaction was employed with both the reactants without methyl iodide to form triazine-3-thiol derivative, the reaction time increased in comparison to that of methylthiotriazines.

It was observed that under similar conditions, a wide range of diketones, containing electron-withdrawing as well as electron-donating groups such as halo, methyl, thiomethyl and nitro easily underwent condensation with thiosemicarbazide and methyl iodide to give 5,6-diaryl substituted 1,2,4-triazines in 10–45 min with excellent isolated yields.

Table 3: Screening of different ILs with or without DMSO

Sr. No.	**IL with DMSO (1:10)**	**Time (min)**	**Yield (%)[b]**
1	$Hbim^+BF_4^-$	48	65
2	$Bbim^+Br^-$	15	90
3	$Bmim^+Br^-$	42	65
4	$[BmmIm]^+BF_4^-$	NP[a]	-
5	$Bbim^+Br^-$ only	500	35

[a] No product formation observed on TLC; [b]Isolated yields

The unsymmetrical diketones were also explored for the synthesis of 1,2,4-triazines. In each case a mixture of regioisomers was obtained which was separated by flash chromatography. The predominance of one isomer over the other has been observed depending on the substituent on the aryl ring. When the reaction temperature was increased to 100 ^oC both of the isomers were observed in approximately equal proportions with trace quantities of bishydrazones. When the same reaction was performed at room temperature, only one isomer was obtained with minor quantity of the other one while at 0 ^oC only one isomer was obtained exclusively. This observation can be utilized to synthesize only one isomer selectively by varying the temperature of the reaction. As we intended to use both of these isomers, we performed all the reactions at 70 ^oC. The structures of all newly synthesized compounds were characterized on the basis of IR, ^1H NMR spectral data and elemental analyses. The known compounds were identified by the comparison of their ^1H NMR with those reported in the literature.[9]

The structure of compound **(71)** has been confirmed by its crystal structure (**Fig. 1**, CCDC 969264). Rest of the isomers were assigned their structures on the basis of the crystal structure of compound (**71**) and the ^1H NMR spectral data of compounds (**71** and **84**) and the remaining compounds.

It may be postulated that the inherent Brønsted acidity of the ionic liquid plays an important role in the formation of hydrazone, and high polarity of the solvent mixture serves to *in situ* formation of *S*-methylthiosemicarbazide that facilitates the cycloaddition reaction.

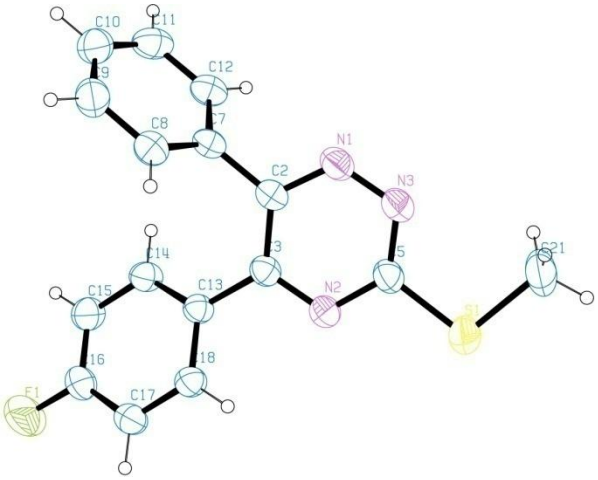
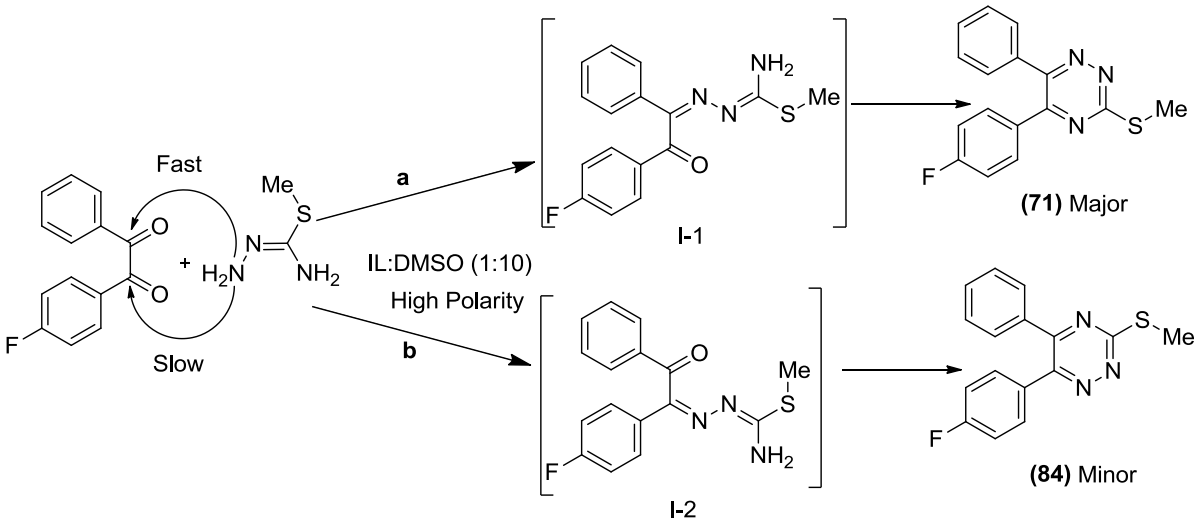


Fig. 1: Crystal structure of compound (**71**) CCDC 969264

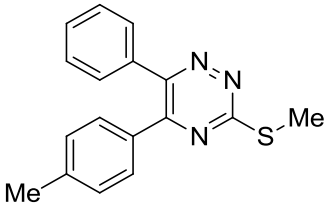
In case of unsymmetrical diketones, a relatively enhanced solvent polarity gave rise to the formation of one hydrazone exclusively by route "**a**" as shown in **Scheme VII**. It would result in the formation of one isomer predominantly. It was reported that the use of highly polar solvents and either acidic/basic conditions might give predominantly one isomer.[7e,10] Due to superior polarity of the said mixture (IL-DMSO) at ambient temperatures in combination with Brønsted acidity of IL one isomer predominantly was obtained achieving the regioselective synthesis at 0 ^{o}C. A mechanism of ionic liquid promoted synthesis has also been postulated. The hydrogen bonding of amine with molecular solvents may hinder the reaction rate, while ionic liquid enhances the reaction rate due to lesser degree of hydrogen bonding and stabilization of transient states. The acidic C_2-H of imidazolium cation could assist carbonyl carbon to have higher electrophilicity resulting into rapid hydrazone formation.



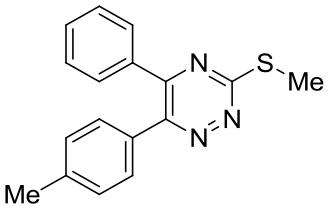
Scheme VII: Plausible mechanism of regioselective synthesis of 1,2,4-triazines in IL:DMSO (1:10)

The methods reported[7] so far for the synthesis of 1,2,4-triazines utilize either acidic conditions using acids such as acetic, hydrochloric, trifluoroacetic and sulfuric orsolvents such as methanol and ethanol requiring very harsh reaction conditions such asrefluxing for 8–24 h. Compared to the reported methods,[7] this method allowed safe,convenient and easy isolation procedures under ambient conditions by simple workup of the reaction mixture in ice cold water. The use of catalytic amounts of ionic liquid in DMSO as a cosolvent is significant as compared to the previously reported method[7f] where excess of ionic liquid was utilized as the reaction medium and promoter. A noteworthy improvement in yields was observed with the current method in comparison to the earlier reported method.[7f] Another advantage of the method reported herein is that a pure regioisomer could be obtained when the reaction is performed at low temperatures.

The IL could be recovered easily from the aqueous filtrate by subjecting it to evaporationon rotary evaporator and removal of DMSO in high vacuum. The recovered IL has been used for the same reaction thrice and showed no loss of its catalytic activity. In conclusion, we have developed a mild, convenient and efficient protocol for the synthesis of 1,2,4-triazines *via* the condensation of diketones, thiosemicarbazide and methyl iodide using a mixture of IL and DMSO (1:10 proportions) as a solvent as well as a promoter. The process gave excellent isolated yields of 1,2,4-triazines in 10–45 min under ambient reaction conditions in shorter reaction times than the earlier reported synthetic procedures.[7f]

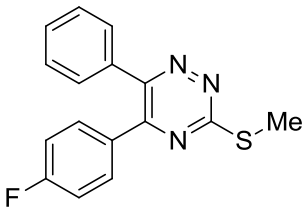


(70)

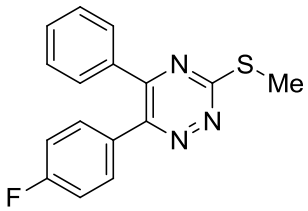


(83)

3-Methylthio-6-phenyl-5-(*p*-tolyl)-1,2,4-triazine **(70)** was obtained as a first fraction from 1-phenyl-2-*p*-tolylethane-1,2-dione **(33)**, thiosemicarbazide **(69)** and methyl iodide in DMSO and $[Bbim]^+Br^-$ in 1:10 (5 g : 0.5 g) proportions after stirring at 70 ^oC for 45 min. Its IR spectrum showed a peak at 1636 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.39 (*s*, 3H, ArC*H*$_3$), 2.78 (*s*, 3H, SC*H*$_3$) and 7.14-7.60 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed (M^+) peak at m/z 293.01. The second fraction was obtained as 3-methylthio-5-phenyl-6-(*p*-tolyl)-1,2,4-triazine **(83)**. Its IR spectrum showed a peak at 1636 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.39 (*s*, 3H, ArC*H*$_3$), 2.79 (*s*, 3H, SC*H*$_3$) and 7.15-7.61 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed molecular ion peak (M^+) at m/z 293.01.

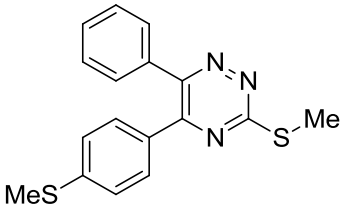


(71)

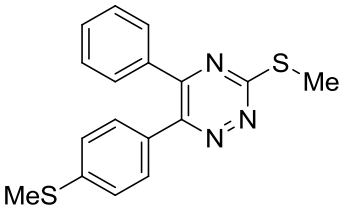


(84)

In a similar fashion, 5-(4-fluorophenyl)-3-methylthio-6-phenyl-1,2,4-triazine **(71)** was obtained as a first fraction from 1-(4-fluorophenyl)-2-phenylethane-1,2-dione **(36)**. Its IR spectrum showed a peak at 1599 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.77 (*s*, 3H, SC*H*$_3$) and 7.05-7.56 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed molecular ion peak (M^+) at m/z296.96. The second fraction was obtained as 6-(4-fluorophenyl)-3-methylthio-5-phenyl-1,2,4-triazine **(84)**. Its IR spectrum showed a peak at 1599 (C=N str) cm^{-1}. Its ^1H NMR showed peaks at δ 2.79 (*s*, 3H, SC*H*$_3$) and 7.02-7.61 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed molecular ion peak (M^+) at m/z 296.96.

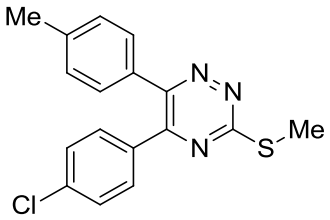


(72)

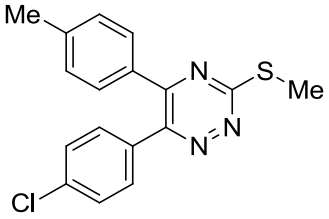


(85)

In a similar fashion, 3-methylthio-5-(4-methylthiophenyl)-6-phenyl-1,2,4-triazine **(72)** was obtained as a first fraction from 1-(4-methylthiophenyl)-2-phenylethane-1,2-dione **(37)**. Its IR spectrum showed a peak at 1590 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.51 (*s*, 3H, ArSC*H*$_3$), 2.78 (*s*, 3H, SC*H*$_3$) and 7.16-7.72 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 324.94. The second fraction was obtained as 3-methylthio-5-phenyl-6-(4-methylthio-phenyl)-1,2,4-triazine **(85)**. Its IR spectrum showed peak at 1590 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.50 (*s*, 3H, ArSC*H*$_3$), 2.77 (*s*, 3H, SC*H*$_3$) and 7.15-7.56 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 324.94.

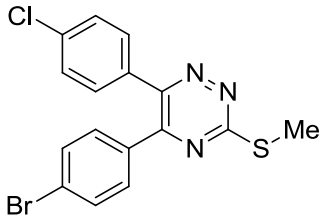


(73)

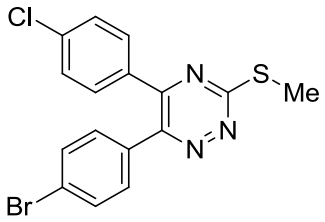


(86)

In the similar fashion, 5-(4-chlorophenyl)-3-methylthio-6-(4-methylphenyl)-1,2,4-triazine **(73)** was obtained as a first fraction from 1-(4-chlorophenyl)-2-*p*-tolylethane-1,2-dione **(38)**. Its IR spectrum showed peak at 1599(C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.32 (*s*, 3H, ArC*H*$_3$), 2.70 (*s*, 3H, SC*H*$_3$) and 7.09-7.52 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) and (M+2) at m/z 326.98 and 328.9 respectively. The second fraction was obtained as 6-(4-chlorophenyl)-3-methylthio-5-(4-methylphenyl)-1,2,4-triazine **(86)**. Its IR spectrum showed peak at 1599 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.41 (*s*, 3H, ArC*H*$_3$), 2.79 (*s*, 3H, SC*H*$_3$) and 7.20-7.56 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) and (M+2) at m/z 326.98 and 329 respectively.

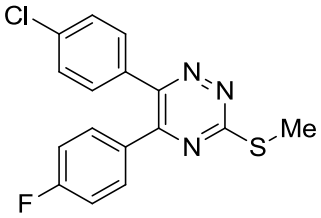


(74)

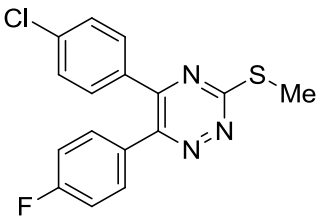


(87)

In the similar fashion, 5-(4-bromophenyl)-6-(4-chlorophenyl)-3-methylthio-1,2,4-triazine **(74)** was obtained as a first fraction from 1-(4-bromophenyl)-2-(4-chlorophenyl)ethane-1,2-dione **(39)**. Its IR spectrum showed a peak at 1588 (C=N str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 2.69 (*s*, 3H, SC*H*$_3$) and 7.27-7.48 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) and (M+2) at m/z 392.83 and 394.8 respectively. The second fraction was obtained as 6-(4-bromophenyl)-5-(4-chlorophenyl)-3-methylthio-1,2,4-triazine **(87)**. Its IR spectrum showed a peak at 1588 (C=N str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 2.69 (*s*, 3H, SC*H*$_3$) and 7.27-7.48 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) and (M+2) at m/z 392.83 and 394.8 respectively.



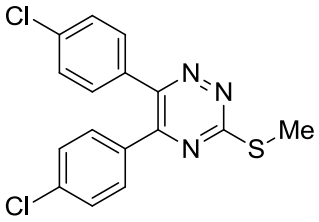
(75)



(88)

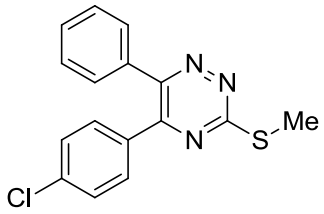
In the similar fashion, 6-(4-chlorophenyl)-5-(4-fluorophenyl)-3-methylthio-1,2,4-triazine **(75)** was obtained as a first fraction from 1-(4-chlorophenyl)-2-(4-fluorophenyl)ethane-1,2-dione **(40)**. Its IR spectrum showed a peak at 1596 (C=N str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 2.68 (*s*, 3H, SC*H*$_3$) and 6.96-7.51 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) and (M+2) at m/z 330.92 and 333 respectively.. The second fraction was obtained as 5-(4-chlorophenyl)-6-(4-fluorophenyl)-3-methylthio-1,2,4-triazine **(88)**. Its IR spectrum showed a peak at 1596 (C=N str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 2.68 (*s*, 3H, SC*H*$_3$) and 6.96-7.51 (*m*, 8H, Ar*H*) ppm. Its ^{13}C NMR showed signals at δ 14.03, 123.83, 128.93, 129.80, 130.31, 131.49, 134.44, 141.78, 148.23, 151.65, 155.61 and 172.41 as a single isomer. Its mass spectrum showed (M^+) and (M+2) at m/z 330.92 and 333 respectively.

5,6-Bis-(4-chlorophenyl)-3-methylthio-1,2,4-triazine **(76)** was obtained from 1,2-bis(4-chlorophenyl)ethane-1,2-dione **(41)**. Its IR spectrum showed a peak at 1591 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.78 (*s*, 3H, SC*H*$_3$) and 7.35-7.54 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) and (M+2) at m/z 346.93 and 348.9 respectively.

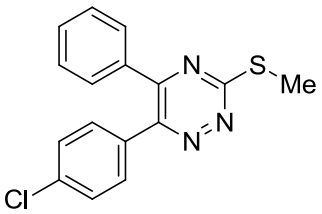


(76)

5-(4-Chlorophenyl)-3-methylthio-6-phenyl-1,2,4-triazine **(77)** was obtained as a first fraction from 1-(4-chlorophenyl)-2-phenylethane-1,2-dione **(42)**. Its IR spectrum showed peaks at 1591 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.79 (*s*, 3H, SC*H*$_3$), 7.19-7.49 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 313.08 and (M+2) at m/z 315.04. The second fraction was obtained as 6-(4-chlorophenyl)-3-methylthio-5-phenyl-1,2,4-triazine **(89)**. Its IR spectrum showed a peak at 1591 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.79 (*s*, 3H, SC*H*$_3$) and 7.32-7.67 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 313.08 and (M+2) at m/z 315.04.



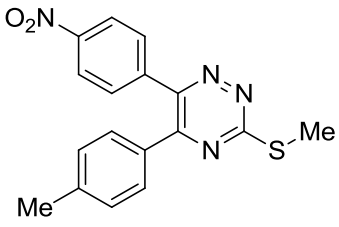
(77)



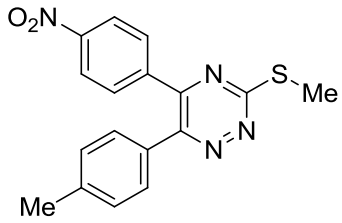
(89)

3-Methylthio-6-(4-nitrophenyl)-5-(*p*-tolyl)-1,2,4-triazine **(78)** was obtained as a first fraction from 1-(4-nitrophenyl)-2-*p*-tolylethane-1,2-dione **(44)**. Its IR spectrum showed peaks at 1602 (C=N str.), and 1523 and 1342 (NO_2) cm^{-1}. Its ^1H NMR showed peaks at δ 2.41 (*s*, 3H, ArC*H*$_3$), 2.79 (*s*, 3H, SC*H*$_3$) and 7.18-8.26 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 338.08. The second fraction was obtained as 3-methylthio-5-(4-nitrophenyl)-6-(*p*-tolyl)-1,2,4-triazine **(90)**. Its IR spectrum showed peaks at 1602 (C=N str.), and 1523 and 1342 (NO_2)

cm^{-1}. Its ^1H NMR showed peaks at δ 2.41 (*s*, 3H, ArC*H*$_3$), 2.79 (*s*, 3H, SC*H*$_3$) and 7.18-8.26 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 338.08.

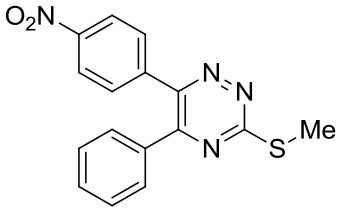


(78)

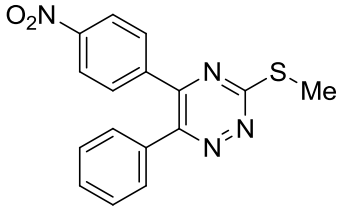


(90)

3-Methylthio-6-(4-nitrophenyl)-5-phenyl-1,2,4-triazine **(79)** was obtained as a first fraction from 1-(4-nitrophenyl)-2-phenylethane-1,2-dione **(45)**. Its IR spectrum showed peaks at 1600 (C=N str), and 1509 and 1347 (NO_2) cm^{-1}. Its ^1H NMR showed peaks at δ 2.79 (*s*, 3H, SC*H*$_3$) and 7.38-8.25 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 324.08. The second fraction was obtained as 3-methylthio-6-phenyl-5-(4-nitrophenyl)-1,2,4-triazine **(91)**. Its IR spectrum showed peaks at 1600 (C=N str.), and 1509 and 1347 (NO_2) cm^{-1}. Its ^1H NMR showed peaks at δ 2.80 (*s*, 3H, SC*H*$_3$) and 7.40-8.25 (*m*, 9H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 324.08.

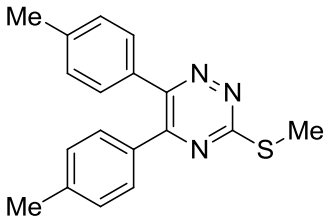


(79)



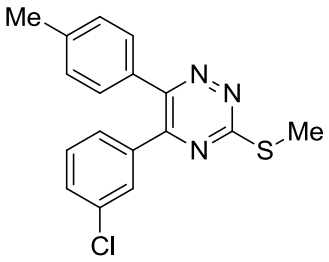
(91)

5,6-Bis-(4-methylphenyl)-3-methylthio-1,2,4-triazine **(80)** was obtained from 1,2-di-*p*-tolylethane-1,2-dione **(46)**. Its IR spectrum showed a peak at 1607 (C=N str.) cm^{-1}. Its ^1H NMR showed signals at δ 2.38 (*s*, 3H, ArC*H*$_3$), 2.40 (*s*, 3H, ArC*H*$_3$), 2.77 (*s*, 3H, SC*H*$_3$) and 7.14-7.50 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 307.02.

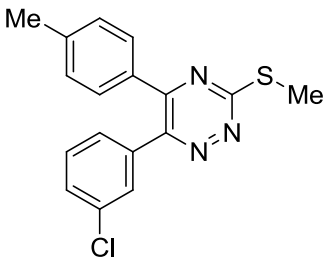


(80)

5-(3-Chlorophenyl)-3-methylthio-6-(*p*-tolyl)-1,2,4-triazine **(81)** was obtained as a first fraction from 1-(3-chlorophenyl)-2-*p*-tolylethane-1,2-dione **(49)**. Its IR spectrum showed a peak at 1609 (C=N str.) cm^{-1}. Its ^1H NMR showed signals at δ 2.40 (*s*, 3H, ArC*H*$_3$), 2.77 (*s*, 3H, SC*H*$_3$) and 7.17-7.66 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) and (M+2) at m/z 326.89 and 329 respectively. The second fraction was obtained as 6-(3-chlorophenyl)-3-methylthio-5-(*p*-tolyl)-1,2,4-triazine **(92)**. Its IR spectrum showed a peak at 1609 (C=N str.) cm^{-1}. Its ^1H NMR showed signals at δ 2.41 (*s*, 3H, ArC*H*$_3$), 2.79 (*s*, 3H, SC*H*$_3$) and 7.19-7.71 (*m*, 8H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 326.89 and (M+2) at m/z 329.01.

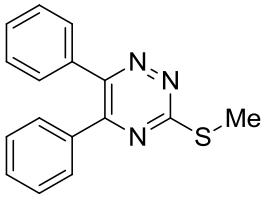


(81)



(92)

5,6-Diphenyl-3-methylthio-1,2,4-triazine **(82)** was obtained from 1,2-diphenyldione /benzil **(50)**. Its IR spectrum showed a peak at 1590 (C=N str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.80 (*s*, 3H, SC*H*$_3$) and 7.34-7.57 (*m*, 10H, Ar*H*) ppm. Its mass spectrum showed (M^+) at m/z 279.01.

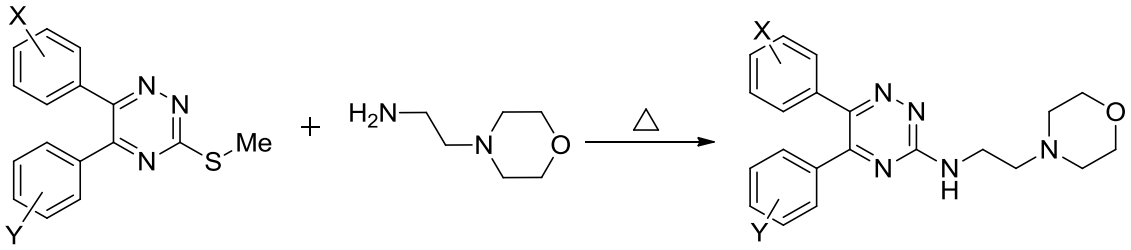


(82)

4.1.3.2. Synthesis of *N*-(2-morpholinoethyl)-1,2,4-triazin-3-amines (94-110)

General method of synthesis

The *S*-methyltriazine compounds were treated with excess of neat 4-(2-aminoethyl)-morpholine (4 eq.) to obtain the desired compounds (**94-110**) as per **Scheme-VIII**. Demethyl-sulfurization and instantaneous amination of *S*-methyltriazine derivatives occurred due to sufficient basicity of morpholinoethylamine without the use of any added base/solvent /catalyst.

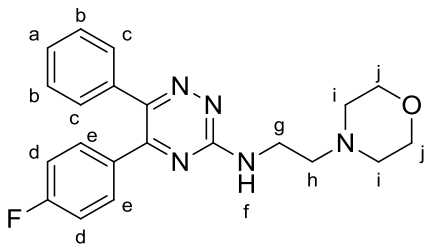


(71, 73-78, 80-82, 84, 86-90, 92) **(93)** **(94-110)**

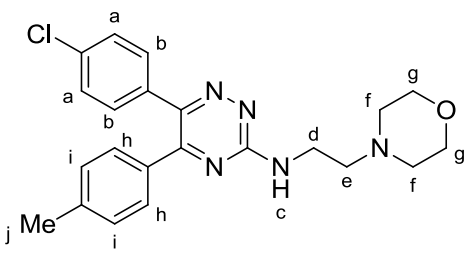
Comp.	X	Y	Comp.	X	Y
(94)	H	4-F	**(103)**	H	H
(95)	4-Cl	4-Me	**(104)**	4-F	H
(96)	4-Cl	4-Br	**(105)**	4-CH_3	4-Cl
(97)	4-Cl	4-F	**(106)**	4-Br	4-Cl
(98)	4-Cl	4-Cl	**(107)**	4-F	4-Cl
(99)	4-Cl	H	**(108)**	H	4-Cl
(100)	4-NO_2	4-Me	**(109)**	4-CH_3	4-NO_2
(101)	4-Me	4-Me	**(110)**	4-CH_3	3-Cl
(102)	3-Cl	4-Me			

Scheme-VIII

5-(4-Fluorophenyl)-*N*-(2-morpholinoethyl)-6-phenyl-1,2,4-triazin-3-amine **(94)** was obtained from 5-(4-fluorophenyl)-3-methylthio-6-phenyl-1,2,4-triazine (**71**). Its IR spectrum showed peaks at 3424 (N-H str.) and1602 (N-H bend.) cm^{-1}. Its ^1H NMR offered signals at δ 6.97-7.58 (m, 9H, ArH_a, ArH_b, ArH_c, ArH_d and ArH_e), 6.05 (bs, 1H, NH_f), 3.55-3.92 (*m*, 6H, H_h and H_j), 2.67-2.70 (*t*, 2H, H_g) and 2.54-2.62 (*t*, 4H, H_i). Its ^{13}C NMR offered peaks at δ 37.64, 53.46, 57.14, 67.00, 115.55, 115.66, 128.50, 129.20, 129.51, 130.38, 131.05, 131.86, 136.31, 156.70, 161.63 and 164.10. Its mass spectrum showed (M^+) and (M+1) at m/z 379.14 and 380.34 respectively.



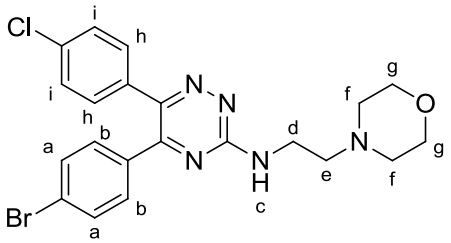
(94)



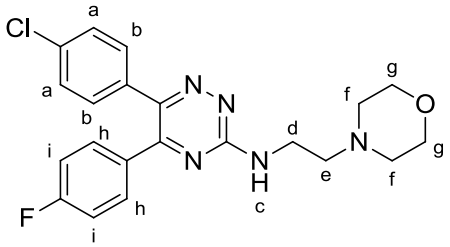
(95)

6-(4-Chlorophenyl)-5-(4-methylphenyl)-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine (**95**) was obtained in the same manner by reacting 6-(4-chlorophenyl)-5-(4-methylphenyl)-3-methylthio-1,2,4-triazine (**73**). Its IR spectrum showed peaks at 3226 (N-H str.), 1594 (N-H bend.) and 1116 (C-O str.) cm^{-1}. Its ^{1}H NMR offered peaks at δ 7.05-7.38 (*m*, 8H, ArH_a, ArH_b, ArH_h and ArH_i), 5.93 (*bs*, 1H, NH_c), 3.62-3.68 (*m*, 6H, H_d and H_g), 2.60-2.63 (*t*, 2H, H_e), 2.45-2.47 (*t*, 4H, H_f) and 2.29 (*s*, 3H, ArCH_{3j}). Its ^{13}C NMR showed peaks at δ 21.35, 37.65, 53.46, 57.15, 67.01, 128.65, 129.05, 129.26, 130.99, 133.19, 135.05, 136.52, 138.48, 149.51, 155.56 and 160.34. Its mass spectrum showed (M^+) and (M+2) at m/z 409.6 and 411.4 respectively.

5-(4-Bromophenyl)-6-(4-chlorophenyl)-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine **(96)** was afforded from 5-(4-bromophenyl)-6-(4-chlorophenyl)-3-methylthio-1,2,4-triazine (**74**). Its IR spectrum showed peaks at 3441(N-H str.), 1601 (N-H bend.) and 1114 (C-O str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 7.26-7.48 (*m*, 8H, ArH_a, ArH_b, ArH_h and ArH_i), 6.10 (*bs*, 1H, NH_c), 3.56-3.74 (*m*, 6H, H_d and H_g), 2.66-2.69 (*t*, 2H, H_e) and 2.50-2.54 (*t*, 4H, H_f). Its mass spectrum showed (M^+) and (M+2) at m/z 474.04 and 476.11 respectively.



(96)

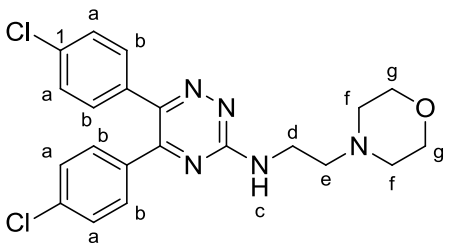


(97)

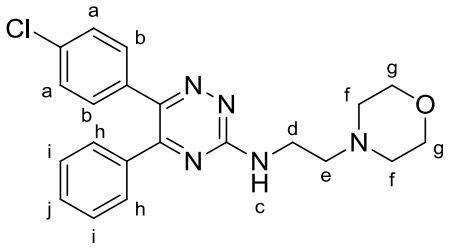
6-(4-Chlorophenyl)-5-(4-fluorophenyl)-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine **(97)** was afforded from 6-(4-chlorophenyl)-5-(4-fluorophenyl)-3-methylthio-1,2,4-triazine (**75**). Its IR spectrum showed peaks at 3448 (N-H str.), 1598 (N-H bend.) and 1115 (C-O str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 7.00-7.50 (*m*, 8H, ArH_a, ArH_b, ArH_h and ArH_i), 6.11 (*bs*, 1H, NH_c), 3.70-3.75 (*m*, 6H, H_d and H_g), 2.67-2.70 (*t*, 2H, H_e) and 2.52-2.54 (*t*, 4H, H_f). Its ^{13}C NMR showed peaks at δ 37.59, 53.39, 57.05, 66.90, 115.56, 115.68, 128.71, 130.38, 130.89, 131.65, 134.65, 136.67, 148.36, 155.43, 162.77 and 165.27. Its mass spectrum showed (M^+) and (M+2) at m/z 413.54 and 415.54 respectively.

5,6-Bis-(4-chlorophenyl)-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine **(98)** was obtained in the same manner from 5,6-bis-(4-chlorophenyl)-3-methylthio-1,2,4-triazine (**76**). Its IR

spectrum showed peaks at 3223(N-H str.), 1595 (N-H bend.) and 1088 (C-O str.) cm^{-1}. Its ^1H NMR showed peaks at δ 7.21-7.37 (*m*, 8H, ArH_a and ArH_b), 6.03 (*bs*, 1H, NH_c), 3.60-3.68 (*m*, 6H, H_d and H_g), 2.60-2.63 (*t*, 2H, H_e) and 2.45-2.47 (*t*, 4H, H_f). Its mass spectrum showed (M^+) and (M+2) at m/z 429.4 and 431.5 respectively.



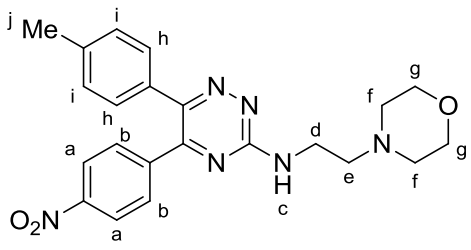
(98)



(99)

6-(4-Chlorophenyl)-*N*-(2-morpholinoethyl)-5-phenyl-1,2,4-triazin-3-amine (**99**) was afforded in the same manner by reacting 6-(4-chlorophenyl)-3-methylthio-5-phenyl-1,2,4-triazine (**77**). Its IR spectrum showed peaks at 3441 (N-H str.), 1596 (N-H bend.) and 1115 (C-O str.) cm^{-1}. Its ^1H NMR showed peaks at δ 7.27-7.51 (*m*, 9H, ArH_a, ArH_b, ArH_h, ArH_i and ArH_j), 6.07 (*bs*, 1H, NH_c), 3.71-3.76 (*m*, 6H, H_d & H_g), 2.66-2.69 (*t*, 2H, H_e) and 2.52-2.54 (*t*, 4H, H_f). Its mass spectrum showed (M^+) and (M+2) at m/z 395.01 and 397.41 respectively.

N-(2-Morpholinoethyl)-5-(4-nitrophenyl)-6-*p*-tolyl-1,2,4-triazin-3-amine (**100**) was obtained in the same manner by reacting 3-methylthio-5-(4-nitrophenyl)-6-*p*-tolyl-1,2,4-triazine (**78**). Its IR spectrum showed peaks at 3440 (N-H str.), 1516 (N-H bend.) and 1115 (C-O str.) cm^{-1}. Its ^1H NMR showed peaks at δ 7.13-8.17 (*m*, 8H, ArH_a, ArH_b, ArH_h and ArH_i), 6.22 (*bs*, 1H, NH_c), 3.73-3.75 (*m*, 6H, H_d & H_g), 2.67-2.70 (*t*, 2H, H_e), 2.52-2.56 (*t*, 4H, H_f) and 2.38 (*s*, 3H, ArCH_{3j}). Its mass spectrum showed (M^+) at m/z 420.52.



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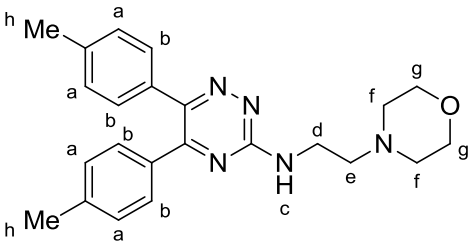
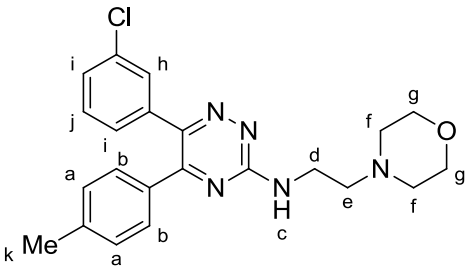


(101)

5,6-Bis-(4-methylphenyl)-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine (**101**) was obtained in similar way by reacting 5,6-bis-(4-methylphenyl)-3-methylthio-1,2,4-triazine (**80**) with excess of neat 4-(2-aminoethyl)-morpholine (**93**). Its IR spectrum offered peaks at 3221

(NH str.), 1595(N-H bend.) and 1115 (C-O str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 7.03-7.32 (*m*, 8H, ArH_a and ArH_b), 5.91 (*bs*, 1H, NH_c), 3.60-3.67 (*m*, 6H, H_d and ArH_g), 2.58-2.61 (*t*, 2H, H_e), 2.44-2.46 (*t*, 4H, H_f) and 2.27 (*s*, 6H, ArCH_{3h}). Its ^{13}C NMR showed peaks at δ 21.30, 21.44, 37.63, 53.43, 57.20, 66.96, 129.01, 129.27, 129.50, 133.67, 138.06, 140.50, 149.62, 156.58 and 160.22. Its mass spectrum showed (M^+) at m/z 390.5.

6-(3-Chlorophenyl)-*N*-(2-morpholinoethyl)-5-*p*-tolyl-1,2,4-triazin-3-amine (**102**) was obtained in the same manner by reacting 6-(3-chlorophenyl)-3-methylthio-5-*p*-tolyl-1,2,4-triazine (**81**). Its IR spectrum showed peaks at 3447 (N-H str.), 1595 (N-H bend.) and 1117 (C-O str.) cm^{-1}. Its ^{1}H NMR offered signals at δ 7.12-7.55 (*m*, 8H, ArH_a, ArH_b, ArH_i and ArH_j), 6.09 (*bs*, 1H, NH_c), 3.70-3.74 (*m*, 6H, H_d & H_g), 2.66-2.69 (*t*, 2H, H_e), 2.52-2.54 (*t*, 4H, H_f) and 2.36 (*s*, 3H, ArCH_{3k}). Its ^{13}C NMR showed peaks at δ 21.45, 37.60, 53.41, 57.11, 66.95, 127.40, 128.28, 129.07, 129.17, 129.39, 129.48, 133.03, 134.31, 138.46, 140.94, 148.27, 156.74 and 160.34. Its mass spectrum showed (M^+) and (M+2) at m/z 409.02 and 411.37 respectively.



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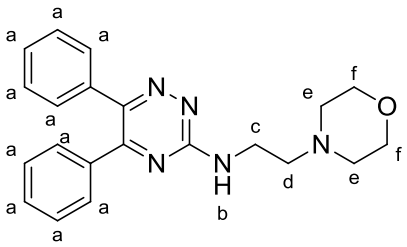
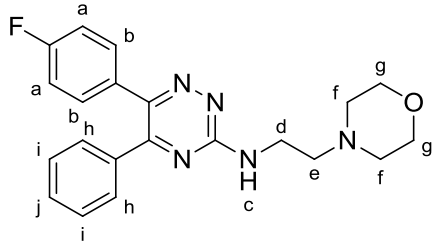


(103)

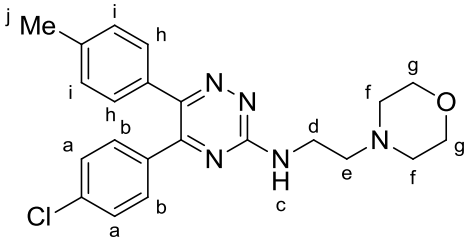
5,6-Diphenyl-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amines (**103**) was obtained by reacting 5,6-diphenyl-3-methylthio-1,2,4-triazine (**82**) with excess of neat 4-(2-aminoethyl)-morpholine (**93**). Its IR spectrum showed peaks at 3223 (N-H str.), 1580 (N-H bend.) and 1114 (C-O str.) cm^{-1}. Its ^{1}H NMR gave peaks at δ 7.20-7.41 (*m*, 10H, ArH_a), 5.97 (*bs*, 1H, NH_b), 3.58-3.68 (*m*, 6H, H_c and H_f), 2.60-2.63 (*t*, 2H, H_d) and 2.45-2.47 (*t*, 4H, H_e). Its ^{13}C NMR showed peaks at δ 37.65, 53.44, 57.16, 66.99, 128.33, 129.22, 129.56, 130.24, 136.37, 136.45, 149.67, 156.79 and 160.29. Its mass spectrum showed (M^+) at m/z 362.4.

6-(4-Fluorophenyl)-*N*-(2-morpholinoethyl)-5-phenyl-1,2,4-triazin-3-amine (**104**) was obtained in the same manner by reacting 6-(4-fluorophenyl)-3-methylthio-5-phenyl-1,2,4-triazine (**84**) with the amine (**93**). Its IR spectrum showed peaks at 3434 (N-H str.), 1602 (N-H bend.) and 1186 (C-O str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 6.96-7.56 (*m*, 9H, ArH_a, ArH_b, ArH_h, ArH_i and ArH_j), 6.09 (*bs*, 1H, NH_c), 3.70-3.74 (*m*, 6H, H_d & H_g), 2.66-2.69 (*t*, 2H, H_e) and

2.45-2.53 (*t*, 4H, H_f). Its ^{13}C NMR showed peaks at δ 37.61, 53.41, 57.10, 66.99, 115.40, 115.61, 128.45, 129.16, 130.33, 130.92, 131.35, 131.73, 136.27, 156.70, 161.63 and 164.10. Its mass spectrum showed (M^+) at m/z 379.28.



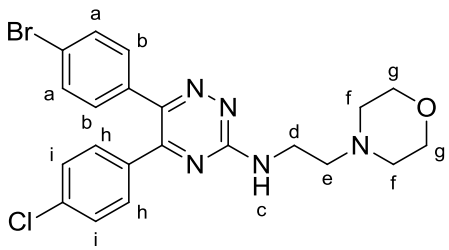
(104)



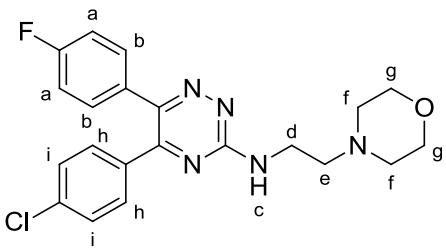
(105)

5-(4-Chlorophenyl)-6-(4-methylphenyl)-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine (**105)** was synthesized from 5-(4-chlorophenyl)-6-(4-methylphenyl)-3-methylthio-1,2,4-triazine (**86**). Its IR spectrum showed peaks at 3225 (NH str.), 1595 (NH bend.) and 1118 (C-O str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 7.05-7.31 (*m*, 8H, ArH_a, ArH_b, ArH_h and ArH_i), 5.94 (*bs*, 1H, NH_c), 3.62-3.67 (*m*, 6H, H_d and H_g), 2.59-2.62 (*t*, 2H, H_e), 2.44-2.47 (*t*, 4H, H_f) and 2.29 (*s*, 3H, ArCH_{3j}). Its mass spectrum showed (M^+) and (M+2) at m/z 409.7 and 411.7 respectively.

6-(4-Bromophenyl)-5-(4-chlorophenyl)-*N*-(2-morpholino-ethyl)-1,2,4-triazin-3-amine (**106**) was prepared in the same manner by reacting 6-(4-bromophenyl)-5-(4-chlorophenyl)-3-methylthio-1,2,4-triazine (**87**) with amine (**93**). Its IR spectrum showed peaks at 3440 (N-H str.), 1602 (N-H bend.) and 1114 (C-O str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 7.26-7.46 (*m*, 8H, ArH_a, ArH_b, ArH_h and ArH_i), 6.11 (*bs*, 1H, NH_c), 3.57-3.73 (*m*, 6H, H_d & H_g), 2.65-2.69 (*t*, 2H, H_e) and 2.50-2.54 (*t*, 4H, H_f). Its mass spectrum showed (M^+) and (M+2) at m/z 473.83 and 476 respectively.



(106)

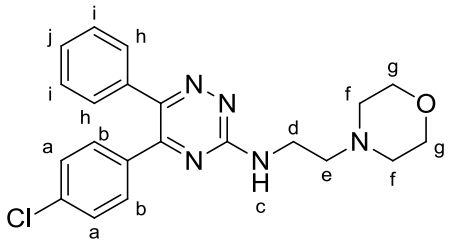


(107)

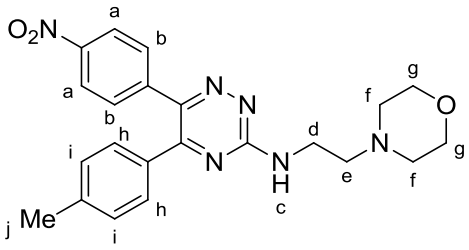
5-(4-Chlorophenyl)-6-(4-fluorophenyl)-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine (**107**) was afforded in the same manner by reacting 5-(4-chlorophenyl)-3-methylthio-6-(4-fluorophenyl)-1,2,4-triazine (**88**). Its IR spectrum showed peaks at 3420 (N-H str.), 1603 (N-H

bend.) and 1116 (C-O str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 7.00-7.48 (*m*, 8H, ArH_a, ArH_b, ArH_h and ArH_i), 6.09 (*bs*, 1H, NH_c), 3.68-3.73 (*m*, 6H, H_d & H_g), 2.67-2.69 (*t*, 2H, H_e) and 2.52-2.54 (*t*, 4H, H_f). Its ^{13}C NMR showed peaks at δ 37.58, 53.40, 57.03, 66.94, 115.58, 115.79, 128.71, 130.38, 130.97, 131.65, 132.16, 134.73, 136.70, 148.31, 162.79 and 165.30. Its mass spectrum showed (M^+) and (M+2) at m/z 413.37 and 415.28 respectively.

5-(4-Chlorophenyl)-*N*-(2-morpholinoethyl)-6-phenyl-1,2,4-triazin-3-amine **(108)** was obtained from 5-(4-chlorophenyl)-3-methylthio-6-phenyl-1,2,4-triazine (**89**). Its IR spectrum showed peaks at 3440 (N-H str.), 1584 (N-H bend.) and 1119 (C-O str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 7.26-7.47 (*m*, 9H, ArH_a, ArH_b, ArH_h, ArH_i and ArH_j), 6.08 (*bs*, 1H, NH_c), 3.55-3.73 (*m*, 6H, H_d & H_g), 2.67-2.69 (*t*, 2H, H_e) and 2.52-2.54 (*t*, 4H, H_f). Its ^{13}C NMR showed peaks at δ 37.60, 53.40, 57.07, 66.96, 128.49, 128.56, 129.44, 130.39, 130.43, 134.41, 134.83, 136.16, 148.53, 156.70 and 162.79. Its mass spectrum showed (M^+) and (M+2) at m/z 395.41 and 397.27 respectively.

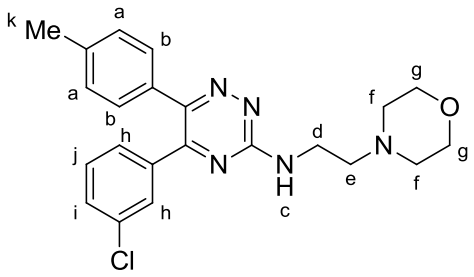


(108)



(109)

N-(2-Morpholinoethyl)-6-(4-nitrophenyl)-5-*p*-tolyl-1,2,4-triazin-3-amine **(109)** was afforded from 3-methylthio-6-(4-nitrophenyl)-5-*p*-tolyl-1,2,4-triazine (**90**). Its IR spectrum showed peaks at 3432 (N-H str.), 1585 (N-H bend.), 1115 (C-O str.), and 1516 and 1340 (NO_2) cm^{-1}. Its ^{1}H NMR showed peaks at δ 7.13-8.19 (*m*, 8H, ArH_a, ArH_b, ArH_h and ArH_i), 6.22 (*bs*, 1H, NH_c), 3.71-3.76 (*m*, 6H, H_d & H_g), 2.68-2.71 (*t*, 2H, H_e), 2.54-2.56 (*t*, 4H, H_f) and 2.38 (*s*, 3H, ArCH_{3j}). Its ^{13}C NMR showed peaks at δ 21.38, 37.58, 53.39, 57.01, 66.88, 123.53, 129.02, 129.68, 130.62, 132.73, 138.86, 141.37, 143.15, 147.43, 153.54 and 160.23. Its mass spectrum showed (M^+) at m/z 420.26.



(110)

5-(3-Chlorophenyl)-*N*-(2-morpholinoethyl)-6-*p*-tolyl-1,2,4-triazin-3-amine **(110)** was prepared from 5-(3-chlorophenyl)-3-methylthio-6-*p*-tolyl-1,2,4-triazine (**92**). Its IR spectrum showed peaks at 3450 (N-H str.), 1596 (N-H bend.) and 1117 (C-O str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 7.12-7.38 (*m*, 8H, ArH_a, ArH_b and ArH_j), 7.55 (*s*, 1H, ArH_h), 6.06 (*bs*, 1H, NH_c), 3.68-3.74 (*m*, 6H, H_d & H_g), 2.66-2.69 (*t*, 2H, H_e), 2.52-2.54 (*t*, 4H, H_f) and 2.36 (*s*, 3H, ArCH_{3k}). Its mass spectrum showed (M^+) and (M+2) at m/z 409.56 and 411.25 respectively.

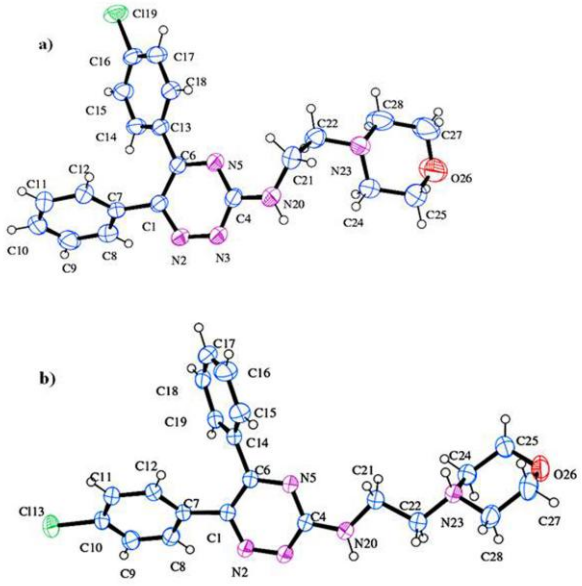


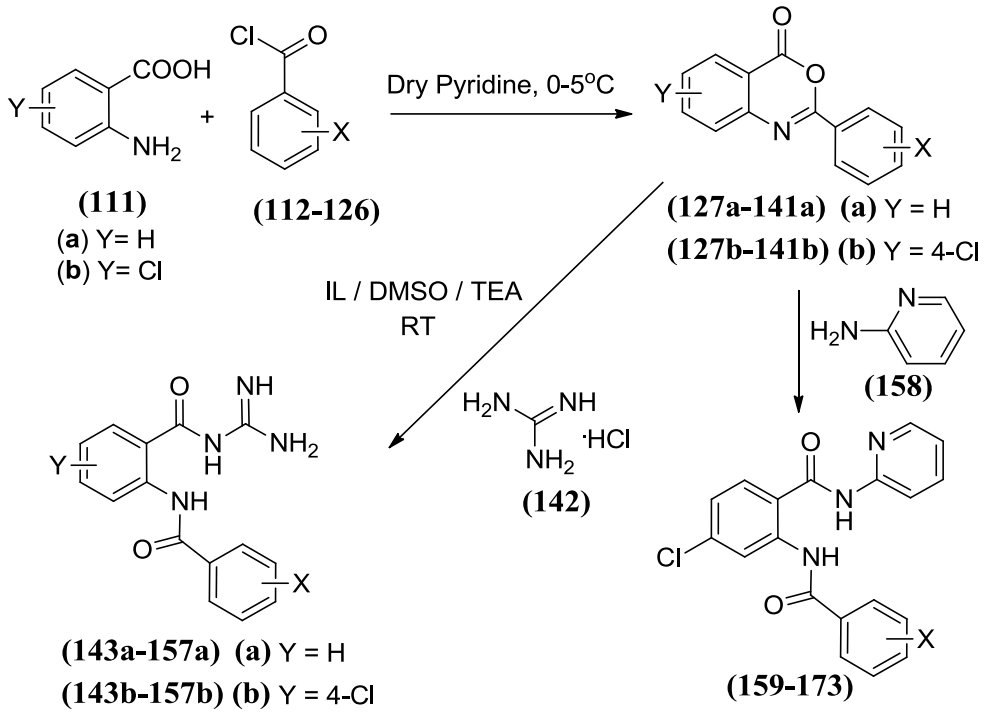
Fig. 2. ORTEPs of single crystals of a) compound (**108)** (CCDC 1028877) and **b**) compound (**99)** (CCDC 1028686) respectively.

The structures of the two compounds (**108)** and **(99)** were also confirmed by their X-ray crystal structures (**Fig. 2**) and the same were submitted to Cambridge Crystallography Database with CCDC 1028877 and CCDC 1028686 respectively.

4.1.4. Synthesis of 2- and 7-substituted 4*H*-benzo[*d*][1,3]oxazin-4-one derivatives (127a-141a and 127b-141b)

4.1.4.1. Synthesis of 2-substituted 4*H*-benzo[*d*][1,3]oxazin-4-ones (127a-141a)

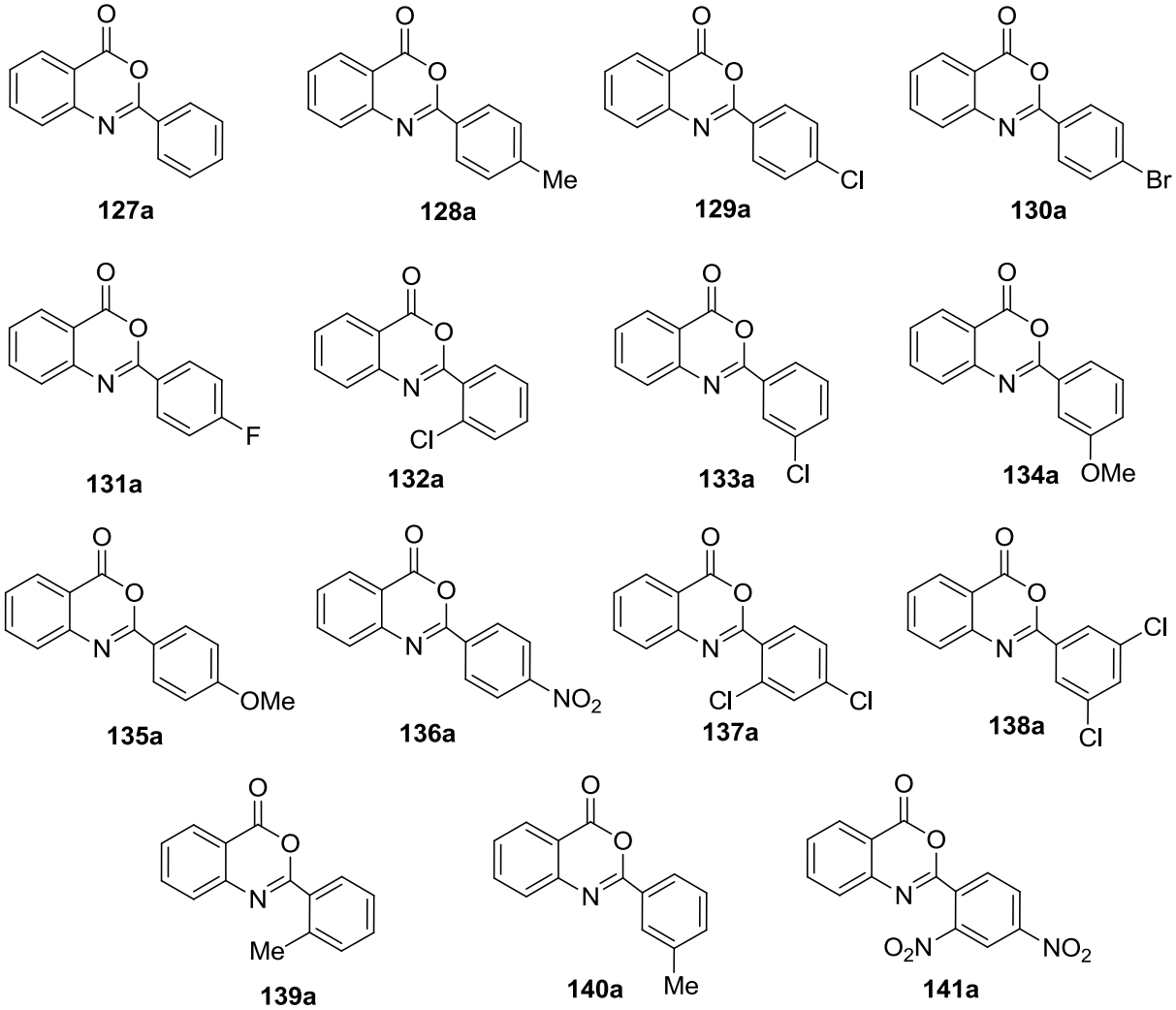
2-Substituted 4*H*-benzo[*d*][1,3]oxazin-4-ones **(127a-141a)** were synthesized by reacting anthranilic acid **(111a)** with different substituted acid chlorides **(112-126)** in dry pyridine at 0-5 °C. The acid chlorides were prepared from substituted benzoic acids with thionyl chloride under reflux conditions till TLC was negative for the parent acid. The solids 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones **(127a-141a)** so obtained were recrystallized with acetone to afford



Comp.	X	Comp.	X
(112, 127, 143, 159)	H	**(120, 135, 151, 167)**	4-OMe
(113, 128, 144, 160)	4-Me	**(121, 136, 152, 168)**	4-NO_2
(114, 129, 145, 161)	4-Cl	**(122, 137, 153, 169)**	2,4-Cl_2
(115, 130, 146, 162)	4-Br	**(123, 138, 154, 170)**	3,5-Cl_2
(116, 131, 147, 163)	4-F	**(124, 139, 155, 171)**	2-Me
(117, 132, 148, 164)	2-Cl	**(125, 140, 156, 172)**	3-Me
(118, 133, 149, 165)	3-Cl	**(126, 141, 157, 173)**	3,5-diNO_2
(119, 134, 150, 166)	3-OMe		

Scheme-IX

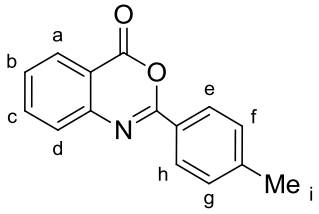
the desired oxazinones, as shiny colourless white to yellow crystals as per **Scheme IX**. All of these compounds have been previously reported from our laboratory and were confirmed by their melting points and IR spectra.



All of the benzoxazinone derivatives **(127a-141a)** showed characteristic stretching vibrations at about 1770-1750 cm^{-1} for the carbonyl of the lactones in their respective IR spectra. The absence of amino group stretching further confirmed the structures of the prepared benzoxazinones.

One representative compound 2-*p*-tolyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(128a)** was further confirmed by its ^{1}H NMR spectrum. It displayed signals at δ 8.14-8.16 (*d*, 1H, *J* = 8.0, ArH_a), 8.09-8.11 (*dd*, 2H, *J* = 8.4, ArH_e and ArH_h), 7.93-7.97 (*m*, 1H, ArH_b), 7.70-7.72 (*d*, 1H, *J* = 8.0, ArH_d), 7.59-7.64 (*m*, 1H, ArH_c), 7.41-7.43 (*dd*, 2H, *J* = 8.0, ArH_f & ArH_g), 2.42 (*s*, 3H,

ArCH_{3i}). Interstingly, the aromatic protons at ArH_a, ArH_b and ArH_c showed vicinal coupling with adjacent protons. All other known derivatives were assigned their structures by comparing their melting points and IR as per their literature reports.



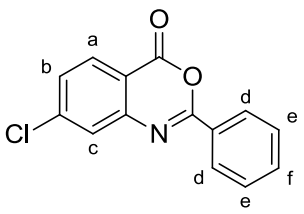
(128a)

4.1.4.2. Synthesis of 7-chloro-2-substituted 4*H*-benzo[*d*][1,3]oxazin-4-ones (127b-141b)

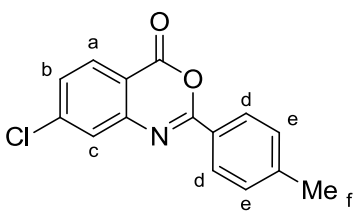
7-Chloro-2-substituted 4*H*-benzo[*d*][1,3]oxazin-4-ones **(127b-141b)** were synthesized by 4-chloroanthranilic acid **(111b)** and diiferent substituted acid chlorides **(112-126)** in dry pyridine at 0-5 °C. The acid chlorides were prepared from substituted benzoic acids with thionyl chloride in reflux conditions till completion of the reaction on TLC. The solids obtained after aqueous workup, were recrystallized with acetone to afford, as shiny colourless white to yellow crystals of compounds (**127b-141b**). All of these compounds were confirmed by their IR, ^{1}H NMR, elemental analysis and mass spectra.

All of them showed characteristic stretching vibrations at about 1770-1750 cm^{-1} for thecarbonyl of lactone in their respective IR spectra along with sharp peak of C-Cl at around 770 cm^{-1}. The absence of stretching of amino group of starting anthranilic acid confirmed the structure of prepared 7-chlorobenzoxazinones.

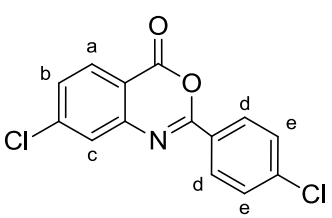
7-Chloro-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(127b)** was synthesized from benzoic acid**(112)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1756 (C=O str.), 1024 (C-O str.) and 778 (C-Cl str.) cm^{-1}. Its ^{1}H NMR offered signals at δ 7.47-7.49 (*dd*, 1H, ArH_b), 7.51-7.54 (*m*, 2H, ArH_e), 7.58-7.60 (*m*, 1H, ArH_f), 7.7108-7.7156 (*d*, 1H, ArH_c), 8.16-8.18 (*d*, 1H, ArH_a) and 8.29-8.32 (*m*, 2H, ArH_d). Its mass spectrum showed (M^+) and (M+2) at m/z 257.41 and 259.43 respectively.



(127b)



(128b)



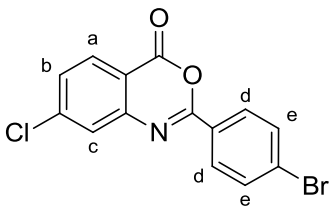
(129b)

Similarly, 7-chloro-2-*p*-tolyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(128b)** was obtained from 4-methylbenzoic acid **(113)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum gave peaks at 1751 (C=O str.), 1021(C-O str.) and 773 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.44 (*s*, 3H, $ArCH_{3f}$), 7.30-7.32 (*d*, 2H, ArH_e), 7.43-7.45 (*dd*, 1H, ArH_b), 7.66-7.67 (*d*, 1H, ArH_c), 8.13-8.15 (*d*, 1H, ArH_a) and 8.16-8.18 (*m*, 2H, ArH_d). Its mass spectrum showed (M^+) and (M+2) at m/z 271.55 and 273.05 respectively.

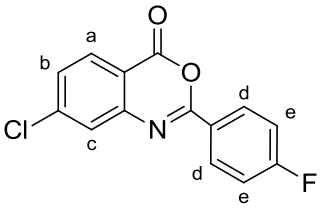
In the same way, 7-chloro-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(129b)** was prepared from 4-chlorobenzoic acid **(114)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1764 (C=O str.), 1011 (C-O str.) and 775 (C-Cl str.) cm^{-1}. Its ^1H NMR gave signals at δ 7.50-7.52 (*dd*, 1H, ArH_b), 7.68-7.69 (*d*, 1H, ArH_c), 8.05-8.09 (*m*, 2H, ArH_e), 8.15-8.17 (*d*, 1H, ArH_a) and 8.22-8.25 (*m*, 2H, ArH_d). Its mass spectrum showed (M^+), (M+2) and (M+4) at m/z 291.50, 293.43 and 295.80 respectively.

2-(4-Bromophenyl)-7-chloro-4*H*-benzo[*d*][1,3]oxazin-4-one **(130b)** was synthesized from 4-bromobenzoic acid **(115)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1754 (C=O str.), 1011 (C-O str.) and 775 (C-Cl str.) cm^{-1}. Its ^1H NMR offered signals at δ 7.40-7.42 (*dd*, 1H, ArH_b), 7.56-7.60 (*m*, 2H, ArH_e), 7.6125-7.6177 (*d*, 1H, ArH_c) and 8.06-8.09 (*m*, 3H, ArH_a and ArH_d). Its mass spectrum showed (M^+) and (M+2) at m/z 336.80 and 338.38 respectively.

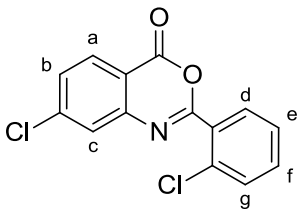
Similarly, 7-chloro-2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(131b)** was obtained from 4-fluorobenzoic acid **(116)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1766 (C=O str.), 1018 (C-O str.) and 778 (C-Cl str.) cm^{-1}. Its ^1H NMR exhibited signals at δ 7.17-7.22 (*m*, 2H, ArH_e), 7.46-7.48 (*dd*, 1H, ArH_b), 7.6729-7.6778 (*d*, 1H, ArH_c), 8.14-8.16 (*d*, 1H, ArH_a) and 8.28-8.33 (*m*, 2H, ArH_d). Its mass spectrum showed (M^+) and (M+2) at m/z 275.36 and 277.60 respectively.



(130b)



(131b)

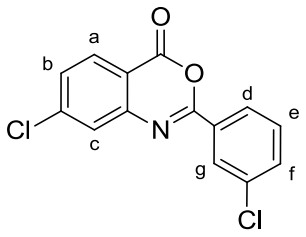


(132b)

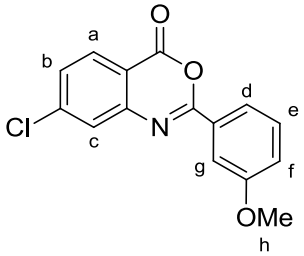
In the same way, 7-chloro-2-(2-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(132b)** was prepared from 2-chlorobenzoic acid **(117)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1764 (C=O str.), 1018 (C-O str.) and 769 (C-Cl str.) cm^{-1}. Its ^1H NMR showed signals at δ 7.39-7.43 (*m*, 1H, ArH_e), 7.46-7.50 (*m*, 1H, ArH_f), 7.52-7.53 (*m*, 1H, ArH_d), 7.54-7.55 (*d*, 1H, ArH_g), 7.7248-7.7298 (*d*, 1H, ArH_c), 7.90-7.92 (*dd*, 1H, ArH_b) and 8.18-8.20 (*d*, 1H, ArH_a). Its mass spectrum showed (M^+), (M+2) and (M+4) at m/z 291.77, 293.92 and 294.75 respectively.

Another derivative, 7-chloro-2-(3-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(133b)** was synthesized from 3-chlorobenzoic acid **(118)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1766 (C=O str.), 1024 (C-O str.) and 776 (C-Cl str.) cm^{-1}. Its ^1H NMR exhibited signals at δ 7.46 (*s*, 1H, ArH_g), 7.48-7.51 (*dd*, 1H, ArH_b), 7.55-7.58 (*d*, 1H, ArH_f), 7.70-7.71 (*d*, 1H, ArH_c), 8.16-8.19 (*dd*, 2H, ArH_a and ArH_d) and 8.29-8.30 (*t*, 1H, ArH_e). Its mass spectrum showed (M^+) and (M+2) at m/z 292.89 and 294 respectively.

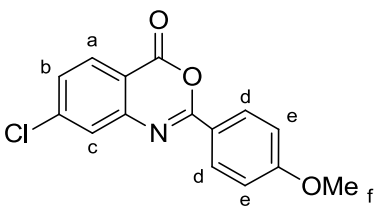
Similarly, 7-chloro-2-(3-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(134b)** was obtained from 3-methoxybenzoic acid **(119)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum gave peaks at 1764 (C=O str.), 1015 (C-O str.) and 778 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 3.90 (*s*, 3H, OCH_{3h}), 6.99-7.01 (*m*, 2H, ArH_e & ArH_f), 7.41-7.44 (*m*, 1H, ArH_b), 7.64-7.65 (*d*, 1H, ArH_c), 8.12-8.14 (*d*, 1H, ArH_a) and 8.23-8.26 (*d*, 2H, ArH_d & ArH_g). Its mass spectrum showed (M^+) and (M+2) at m/z 287.05 and 289.15 respectively.



(133b)



(134b)

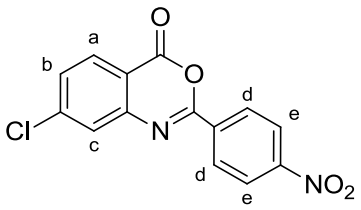


(135b)

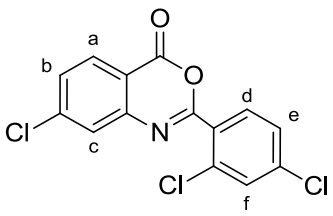
In the same way, 7-chloro-2-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(135b)** was obtained from 4-methoxybenzoic acid **(120)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1758 (C=O str.), 1025 (C-O str.) and 772 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 3.90 (*s*, 3H, OCH_{3f}), 6.98-7.01 (*m*, 2H, ArH_e), 7.41-7.43 (*dd*, 1H, ArH_b),

7.6411-7.6460 (*d*, 1H, ArH_c), 8.12-8.14 (*d*, 1H, ArH_a) and 8.22-8.26 (*m*, 2H, ArH_d). Its mass spectrum showed (M^+) and (M+2) at m/z 287.18 and 289.79 respectively.

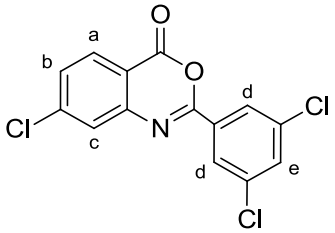
In the same manner, other derivatives, 7-chloro-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]-oxazin-4-one **(136b)** and 7-chloro-2-(2,4-dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(137b)** were synthesized from 4-chloroanthranilic acid **(111b)** with 4-nitrobenzoic acid **(121)** and 2,4-dichlorobenzoic acid **(122)** respectively. The former one (**136b)** showed IR spectrum peaks at 1765 (C=O str.), 1008 (C-O str.), 1526 and 1349 (NO_2) and 777 (C-Cl str.) cm^{-1} while later one (**137b)** showed IR spectrum peaks at 1775 (C=O str.), 1026 (C-O str.) and 776 (C-Cl str.) cm^{-1}.



(136b)



(137b)

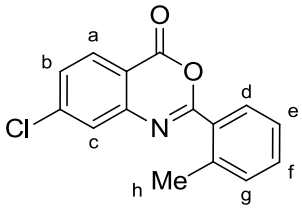


(138b)

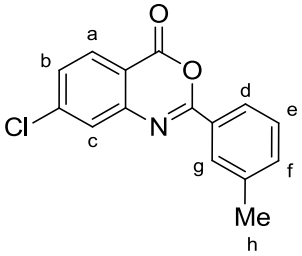
The ^1H NMR spectra of **(136b)** exhibited signals at δ 7.54-7.57 (*dd*, 1H, ArH_b), 7.7522-7.7571 (*d*, 1H, ArH_c), 8.19-8.21 (*d*, 1H, ArH_a), 8.35-8.38 (*m*, 2H, ArH_e), 8.47-8.50 (*m*, 2H, ArH_d), while **(137b)** showed peaks at δ7.38-7.41 (*dd*, 1H, ArH_b), 7.52-7.53 (*d*, 1H, ArH_f), 7.54-7.56 (*m*, 1H, ArH_e), 7.7114-7.7160 (*d*, 1H, ArH_c), 7.89-7.91 (*d*, 1H, ArH_d) and 8.17-8.19 (*d*, 1H, ArH_a). The mass spectra for **(136b)** showed (M^+) and (M+2) at m/z 302.42 and 304 respectively and for **(137b)** showed (M^+) and (M+2) 326.13 and 328.42 respctively.

Similarly, 7-chloro-2-(3,5-dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(138b)** was obtained from 3,5-dichlorobenzoic acid **(123)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1771 (C=O str.), 1009 (C-O str.) and 775 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 7.36-7.42 (*dd*, 1H, ArH_b), 7.52-7.56 (*m*, 2H, ArH_d), 7.7135-7.7183 (*d*, 1H, ArH_c), 7.89-7.91 (*d*, 1H, ArH_e) and 8.17-8.19 (*d*, 1H, ArH_a). Its mass spectrum showed (M^+) and (M+2) at m/z 324.27 and 326.73 respectively.

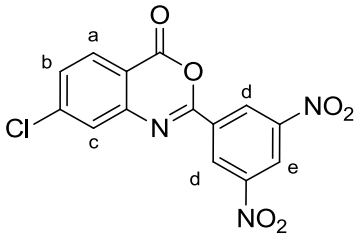
Another derivative, 7-chloro-2-*o*-tolyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(139b)** was obtained from 2-methylbenzoic acid **(124)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1754 (C=O str.), 1025 (C-O str.) and 771 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.72 (s, 3H, $ArCH_{3h}$), 7.31-7.35 (*m*, 2H, ArH_e and ArH_f), 7.41-7.46 (*m*, 1H, ArH_g), 7.47-7.50 (*d*, 1H, ArH_b), 7.68-7.69 (*d*, 1H, ArH_c), 8.03-8.05 (*m*, 1H, ArH_d) and 8.16-8.18 (*d*, 1H, ArH_a). Its mass spectrum showed (M^+) and (M+2) at m/z 271.32 and 273.08 respectively.



(139b)



(140b)



(141b)

Similarly, 7-chloro-2-*m*-tolyl-4*H*-benzo[*d*]-[1,3]oxazin-4-one **(140b)** was obtained from 3-methylbenzoic acid **(125)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1759 (C=O str.), 1022 (C-O str.) and 779 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 2.45 (*s*, 3H, ArCH_{3h}), 7.39-7.40 (*m*, 2H, ArH_e & ArH_f), 7.45-7.47 (*dd*, 1H, ArH_b), 7.68-7.69 (*d*, 1H, ArH_c), 8.08-8.09 (*d*, 1H, ArH_d), 8.11 (*s*, 1H, ArH_g) and 8.14-8.16 (*d*, 2H, ArH_a). Its mass spectrum showed (M^+) and (M+2) at m/z 270.42 and 271.84 respectively.

In the same way, 7-chloro-2-(3,5-dinitrophenyl)-4*H*-benzo-[*d*][1,3]oxazin-4-one **(141b)** was afforded from 3,5-dinitrobenzoic acid **(126)** and 4-chloroanthranilic acid **(111b)**. Its IR spectrum showed peaks at 1769 (C=O str.), 1008 (C-O str.), 1539 and 1346 (NO_2) and 775 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 7.25-7.27 (*dd*, 1H, ArH_b), 8.07-8.09 (*d*, 1H, ArH_a), 8.77-8.78 (*d*, 1H, ArH_c), 9.11-9.13 (*m*, 2H, ArH_d) and 9.24-9.25 (*d*, 1H, ArH_e). Its mass spectrum showed (M^+) and (M+2) at m/z 347.62 and 349.14 respectively.

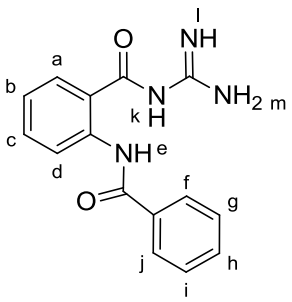
4.1.5. Synthesis of guanido derivatives of anthranilamide

4.1.5.1. Synthesis of 2-substituted *N*-amidinobenzamides (143a-157a)

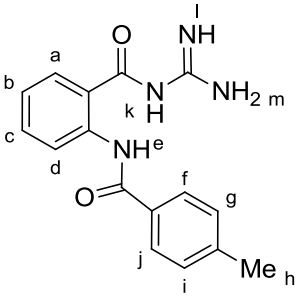
2-Substituted *N*-amidinobenzamides **(143a-157a)** were synthesized from diiferent substituted 4*H*-benzo[*d*][1,3]oxazin-4-ones (**127a-141a)** and guanidine hydrochloride **(142)** using triethylamine as a base in ionic liquid ($Bbim^+$)Br^-:DMSO (**Scheme IX**). The reaction progress was monitored by TLC. The solid obtained after aqueous workup were recrystallized to afford 2-substituted *N*-amidinobenzamides **(143a-157a)**, as white solids. All of these compounds were confirmed by their IR, ^1H NMR, elemental analysis and mass spectra.

All of them showed characteristic vibrations at about 3300-3500 cm^{-1} for the N-H stretching and 1550-1640 cm^{-1} for the N-H bending. All the compounds were confirmed by absence of lactone carbonyl stretching in their respective IR spectra.

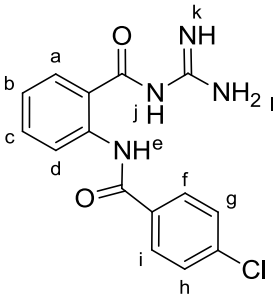
N-Amidino-2-benzoylaminobenzamide **(143a)** was synthesized from 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(127a)**. Its IR spectrum showed peaks at 3417 (N-H str.), 1650 (C=O str.) and 1586 (N-H bend.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 13.70 (*bs*, 1H, NH_k), 8.69-8.71 (*d*, 1H, ArH_a), 8.23-8.25 (*d*, 1H, ArH_d), 8.01-8.04 (*dd*, 2H, ArH_f & ArH_j), 7.75 (*bs*, 2H, NH_{2m}), 7.50-7.58 (*m*, 3H, ArH_g, ArH_h and ArH_i), 7.40-7.43 (*t*, 1H, ArH_b), 7.20 (*bs*, 1H, NH_e), 7.04-7.08 (*t*, 1H, ArH_c) and 6.90 (*bs*, 1H, NH_l). Its mass spectrum showed (M+1) at m/z 283.2.



(143a)



(144a)



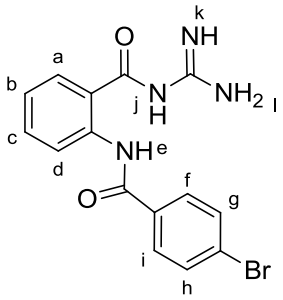
(145a)

Similarly, *N*-amidino-2-(4-methylbenzoylamino)benzamide **(144a)** was obtained from 2-*p*-tolyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(128a)**. Its IR spectrum showed peaks at 3405 (N-H str.), 1653, 1637 (C=O str.) and 1586 (N-H bend.) cm^{-1}. Its ^1H NMR showed peaks at δ 13.59 (*bs*, 1H, NH_k), 8.66-8.68 (*d*, 1H, ArH_a), 8.22-8.23 (*d*, 1H, ArH_d), 7.90-7.92 (*dd*, 2H, ArH_f & ArH_j), 7.70 (*bs*, 2H, NH_{2m}), 7.39-7.42 (*t*, 1H, ArH_b), 7.31-7.33 (*dd*, 2H, ArH_g & ArH_i), 7.20 (*bs*, 1H, NH_e), 7.03-7.07 (*t*, 1H, ArH_c), 6.89 (*bs*, 1H, NH_l) and 2.41 (*s*, 3H, ArCH_{3h}). Its mass spectrum showed (M+1) at m/z 297.2.

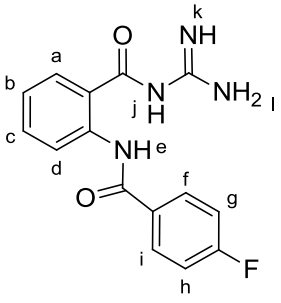
The compound (**145a**) was obtained from 2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(129a)**. Its infrared spectrum showed peaks at 3420 (N-H str.), 1654 (C=O str.) and 1587 (N-H bend.) cm^{-1}. Its ^1H NMR showed peaks at δ 13.70 (*bs*, 1H, NH_j), 8.6411-8.6423 (*d*, 1H, ArH_a), 8.19-8.21 (*d*, 1H, ArH_d), 7.97-8.02 (*dd*, 2H, ArH_f & ArH_i), 7.71 (*bs*, 2H, NH_{2l}), 7.54-7.57 (*dd*, 2H, ArH_g & ArH_h), 7.41-7.46 (*t*, 1H, ArH_b), 7.21 (*bs*, 1H, NH_e), 7.07-7.14 (*t*, 1H, ArH_c) and 7.03 (*bs*, 1H, NH_k). Its mass spectrum showed (M^+) and (M+2) at m/z 316.33 and 318.66 respectively.

In the same manner, *N*-amidino-2-(4-bromobenzoylamino)benzamide **(146a)** was synthesized from 2-(4-bromophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(130a)**. Its IR spectrum showed peaks at 3372 (N-H str.), 1650 (C=O str.), 1588 (N-H bend.) and 760 (C-Br str.) cm^{-1}. Its

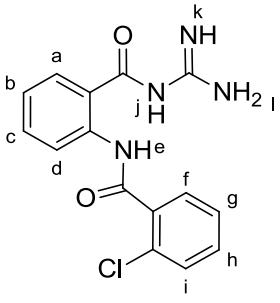
^{1}H NMR spectrum displayed peaks at δ 13.66 (*bs*, 1H, N*H*$_j$), 8.54-8.56 (*d*, 1H, Ar*H*$_a$), 8.23 (*bs*, 1H, N*H*$_e$), 8.11-8.14 (*d*, 1H, Ar*H*$_d$), 7.85-7.88 (*dd*, 2H, Ar*H*$_f$ & Ar*H*$_i$), 7.62-7.64 (*dd*, 2H, Ar*H*$_g$ & Ar*H*$_h$), 7.50 (*bs*, 1H, N*H*$_k$), 7.34-7.38 (*t*, 1H, Ar*H*$_b$), 7.09 (*bs*, 2H, N*H*$_{2l}$) and 6.98-7.03 (*t*, 1H, Ar*H*$_c$). Its mass spectrum showed (M^+) at m/z 361.1.



(146a)



(147a)



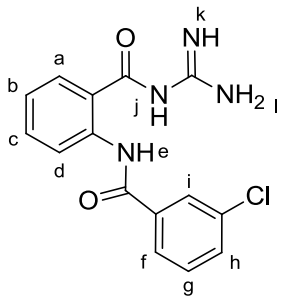
(148a)

In the similar way, *N*-amidino-2-(4-fluorobenzoylamino)benzamide **(147a)** was obtained from 2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(131a)**. Its IR spectrum showed peaks at 3421 (N-H str.), 1653 (C=O str.), 1587 (N-H bend.) and 1355 (C-F str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 13.68 (*bs*, 1H, N*H*$_j$), 8.63-8.65 (*d*, 1H, Ar*H*$_a$), 8.20-8.22 (*d*, 1H, Ar*H*$_d$), 8.05-8.08 (*dd*, 2H, Ar*H*$_f$ & Ar*H*$_i$), 7.86 (*bs*, 2H, N*H*$_{2l}$), 7.41-7.45 (*t*, 1H, Ar*H*$_b$), 7.28-7.32 (*dd*, 2H, Ar*H*$_g$ & Ar*H*$_h$), 7.19 (*bs*, 1H, N*H*$_e$), 7.06-7.10 (*t*, 1H, Ar*H*$_c$) and 6.93 (*bs*, 1H, N*H*$_k$). Its mass spectrum showed (M^+) at m/z 300.12.

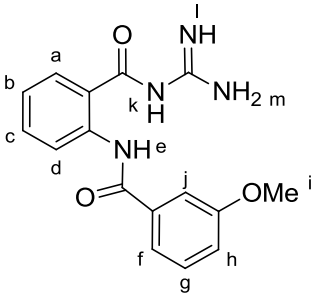
The compound (**148a**) was obtained from 2-(2-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(132a)**. Its IR spectrum showed peaks at 3400 (N-H str.), 1660 (C=O str.), 1605 (N-H bend.) and 765 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 13.38 (*bs*, 1H, N*H*$_j$), 8.62-8.64 (*d*, 1H, Ar*H*$_a$), 8.22-8.25 (*d*, 1H, Ar*H*$_d$), 7.70-7.80 (*bs*, 1H, N*H*$_k$), 7.67-7.69 (*d*, 1H, Ar*H*$_i$), 7.52-7.55 (*t*, 1H, Ar*H*$_b$), 7.42-7.51 (*m*, 3H, Ar*H*$_f$, Ar*H*$_g$ & Ar*H*$_h$), 7.50 (*bs*, 1H, N*H*$_e$), 7.09-7.13 (*t*, 1H, Ar*H*$_c$) and 7.03 (*bs*, 2H, N*H*$_{2l}$). Its mass spectrum showed (M^+) and (M+2) at m/z 316.10 and 318.12 respectively.

Similarly, *N*-amidino-2-(3-chlorobenzoylamino)benzamide **(149a)** was obtained from 2-(3-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(133a)**. Its IR spectrum showed peaks at 3414 (N-H str.), 1654 (C=O str.), 1586 (N-H bend.) and 766 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 13.77 (*bs*, 1H, N*H*$_j$), 8.63-8.65 (*d*, 1H, Ar*H*$_a$), 8.20-8.22 (*d*, 1H, Ar*H*$_d$), 7.94-7.96 (*dd*, 2H, Ar*H*$_f$ & Ar*H*$_i$), 7.77 (*bs*, 2H, N*H*$_{2l}$), 7.59-7.61 (*d*, 1H, Ar*H*$_h$), 7.52-7.56 (*t*, 1H, Ar*H*$_g$), 7.42-

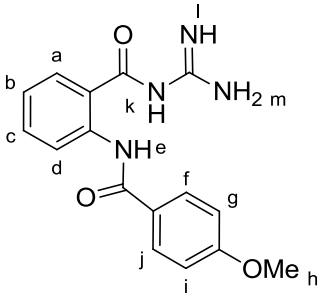
7.46 (*t*, 1H, ArH_b), 7.20 (*bs*, 1H, NH_e), 7.08-7.12 (*t*, 1H, ArH_c) and 6.95 (*bs*, 1H, NH_k). Its mass spectrum showed (M^+) and (M+2) at m/z 316.32 and 318.66 respectively.



(149a)



(150a)

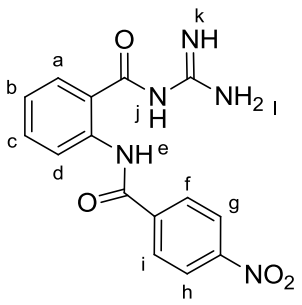


(151a)

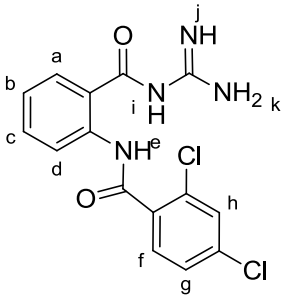
Another compound, *N*-amidino-2-(3-methoxybenzoylamino)benzamide **(150a)** was obtained from 2-(3-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(134a)**. Its IR spectrum showed peaks at 3416 (N-H str.), 1653 (C=O str.) and 1588 (N-H bend.) cm^{-1}. Its ^1H NMR showed peaks at δ 13.64 (*bs*, 1H, NH_k), 8.67-8.69 (*d*, 1H, ArH_a), 8.24-8.26 (*d*, 1H, ArH_d), 7.90 (*bs*, 2H, NH_{2m}), 7.59-7.61 (*d*, 1H, ArH_f), 7.51 (*s*, 1H, ArH_j), 7.43-7.47 (*m*, 2H, ArH_b & ArH_g), 7.35 (*bs*, 1H, NH_e), 7.13-7.15 (*d*, 1H, ArH_h), 7.07-7.11 (*t*, 1H, ArH_c), 6.95 (*bs*, 1H, NH_l) and 3.85 (*s*, 3H, OCH_{3i}). Its mass spectrum showed (M^+) at m/z 312.96.

The compound (**151a**) having 4-methoxy group was obtained from 2-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(135a)**. Its IR spectrum showed peaks at 3418 (N-H str.), 1657 (C=O str.) and 1587 (N-H bend.) cm^{-1}. Its ^1H NMR showed peaks at δ 13.52 (*bs*, 1H, NH_k), 8.77-8.79 (*d*, 1H, ArH_a), 8.20-8.22 (*d*, 1H, ArH_d), 7.93-8.01 (*dd*, 2H, ArH_f & ArH_j), 7.70 (*bs*, 2H, NH_{2m}), 7.29-7.49 (*dd*, 2H, ArH_g & ArH_i), 7.17 (*bs*, 1H, NH_e), 7.00-7.12 (*m*, 2H, ArH_b & ArH_c), 6.69 (*bs*, 1H, NH_l) and 3.85 (*s*, 3H, OCH_{3h}). Its mass spectrum showed (M^+) at m/z 312.22.

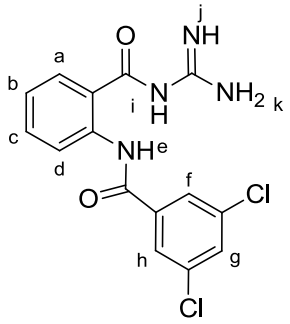
Compound *N*-amidino-2-(4-nitrobenzoylamino)benzamide **(152a)** was obtained from 2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(136a)**. Its IR spectrum showed peaks at 3393 (N-H str.), 1665 (C=O str.), 1591 (N-H bend.), and 1539 and 1343 (NO_2) cm^{-1}. Its ^1H NMR showed peaks at δ 13.95 (*bs*, 1H, NH_j), 8.60-8.62 (*d*, 1H, ArH_a), 8.33-8.36 (*dd*, 2H, ArH_f & ArH_i), 8.21-8.24 (*dd*, 2H, ArH_g & ArH_h), 8.18-8.21 (*d*, 1H, ArH_d), 7.94 (*bs*, 2H, NH_{2l}), 7.44-7.48 (*t*, 1H, ArH_b), 7.30 (*bs*, 1H, NH_e), 7.10-7.14 (*t*, 1H, ArH_c) and 6.99 (*bs*, 1H, NH_k). Its mass spectrum showed (M^+) at m/z 327.33.



(152a)



(153a)

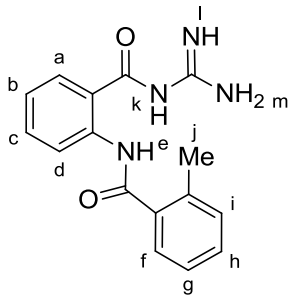


(154a)

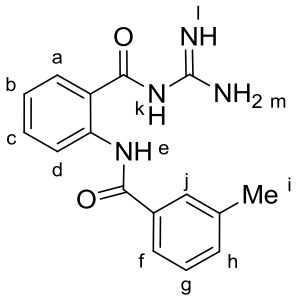
Another compound, *N*-amidino-2-(2,4-dichlorobenzoylamino)benzamide **(153a)** was obtained from 2-(2,4-dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(137a)**. Its IR spectrum showed peaks at 3484 (N-H str.), 1658, 1630 (C=O str.), 1589 (N-H bend.) and 759 (C-Cl str.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 13.53 (*bs*, 1H, NH_i), 8.60-8.62 (*d*, 1H, ArH_a), 8.20-8.22 (*d*, 1H, ArH_d), 7.70-7.72 (*d*, 1H, ArH_f), 7.6436-7.6484 (*d*, 1H, ArH_h), 7.48-7.51 (*d*, 1H, ArH_g), 7.38-7.42 (*t*, 1H, ArH_b), 7.38 (*bs*, 1H, NH_e), 7.19 (*bs*, 1H, NH_j), 7.09-7.12 (*t*, 1H, ArH_c) and 6.95 (*bs*, 2H, NH_{2k}). Its mass spectrum showed (M^+), (M+2) and (M+4) at m/z 351.07, 353.73 and 355.31 respectively.

The compound (**154a**) with 3,5-dichlorophenyl group was obtained from 2-(3,5-dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(138a)**. Its IR spectrum showed peaks at 3393 (N-H bend.), 1665, 1629 (C=O str.), 1591 (N-H bend.) and 768 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 14.31 (*bs*, 1H, NH_i), 9.1101-9.1150 (*d*, 1H, ArH_g), 9.01-9.03 (*d*, 2H, ArH_f & ArH_h), 8.62-8.64 (*d*, 1H, ArH_a), 8.16-8.18 (*d*, 1H, ArH_d), 8.05-8.07 (*bs*, 2H, NH_{2k}), 7.46-7.51 (*t*, 1H, ArH_b), 7.20 (*bs*, 1H, NH_e), 7.15-7.18 (*t*, 1H, ArH_c) and 6.95 (*bs*, 1H, NH_j). Its mass spectrum showed (M^+) at m/z 352.40.

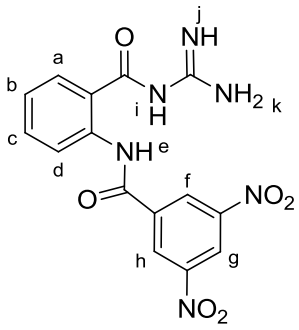
N-Amidino-2-(2-methylbenzoylamino)benzamide **(155a)** was obtained from 2-(2-methylphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(139a)**. Its IR spectrum showed peaks at 3394 (N-H str.), 1667, 1652 (C=O str.), 1601 (N-H bend.) and 760 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 13.33 (*bs*, 1H, NH_k), 8.67-8.69 (*d*, 1H, ArH_a), 8.23-8.26 (*d*, 1H, ArH_d), 7.61-7.63 (*d*, 1H, ArH_f), 7.50 (*bs*, 1H, NH_e), 7.41-7.46 (*t*, 1H, ArH_b), 7.36-7.40 (*t*, 1H, ArH_g), 7.28-7.32 (*m*, 2H, ArH_h & ArH_i), 7.20 (*bs*, 1H, NH_l), 7.05-7.09 (*t*, 1H, ArH_c), 6.95 (*bs*, 1H, NH_{2m}) and 2.48 (*s*, 3H, ArCH_{3j}). Its mass spectrum showed (M^+) at m/z 296.11.



(155a)



(156a)



(157a)

Other derivative, *N*-amidino-2-(3-methylbenzoylamino)benzamide **(156a)** was obtained from 2-(3-methyl-phenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(140a)**. Its IR spectrum showed peaks at 3394 (N-H str.), 1651 (C=O str.) and 1586 (N-H bend.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 13.59 (*bs*, 1H, NH_k), 8.65-8.67 (*d*, 1H, ArH_a), 8.17-8.19 (*d*, 1H, ArH_d), 8.00 (*bs*, 1H, NH_e), 7.80-7.81 (*dd*, 2H, ArH_f & ArH_j), 7.60 (*bs*, 1H, NH_l), 7.44-7.46 (*d*, 1H, ArH_h), 7.39-7.42 (*m*, 2H, ArH_b & ArH_g), 7.07-7.11 (*t*, 1H, ArH_c), 7.01 (*bs*, 2H, NH_{2m}) and 2.41 (*s*, 3H, ArCH_{3i}). Its mass spectrum showed (M^+) at m/z 296.32.

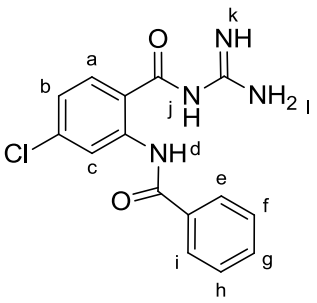
The compound (**157a**) with 3,5-dinitrophenyl group was obtained from 2-(3,5-dinitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(141a)**. Its IR spectrum showed peaks at 3502, 3392 (N-H str.), 1668 (C=O str.), 1593 (N-H bend.) and 1539, 1344 (NO_2) cm^{-1}. Its ^1H NMR showed peaks at δ 14.27 (*bs*, 1H, NH_i), 9.0732-9.0779 (*d*, 1H, ArH_f), 9.01 (*s*, 1H, ArH_g), 8.9711-8.9758 (*d*, 1H, ArH_h), 8.61-8.63 (*d*, 1H, ArH_a), 8.15-8.17 (*d*, 1H, ArH_d), 8.04 (*bs*, 2H, NH_{2k}), 7.47-7.52 (*t*, 1H, ArH_b), 7.45 (*bs*, 1H, NH_e), 7.15-7.19 (*t*, 1H, ArH_c) and 7.03 (*bs*, 1H, NH_j). Its mass spectrum showed (M^+) at m/z 371.53.

4.1.5.2. Synthesis of 4-chloro-2-substituted *N*-amidinobenzamides (143b-157b)

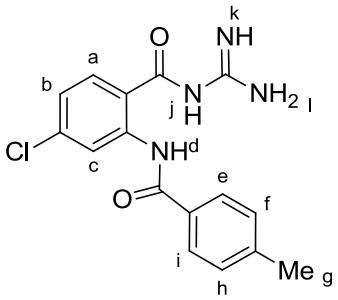
2-Substituted *N*-amidino-4-chlorobenzamides **(143b-157b)** were synthesized from different 7-chloro-2-substituted-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones (**127b-141b)** and guanidine hydrochloride **(142)** using triethylamine as a base in ionic liquid ($Bbim^+$)Br^-:DMSO. The progress of the reaction was monitored by TLC. The solids obtained after aqueous workup were recrystallized from methanol to afford the desired derivatives **(143b-157b)**, as white solids. All of these compounds were confirmed by their IR, ^1H NMR, elemental analysis and mass spectra.

All of them showed characteristic stretching vibrations at about 3300-3500 cm^{-1} for the NH stretching, 1550-1640 cm^{-1} for the N-H bending and also halo stretching at around 700 cm^{-1}. All the compounds were confirmed by absence of lactone carbonyl stretching in their respective IR spectra.

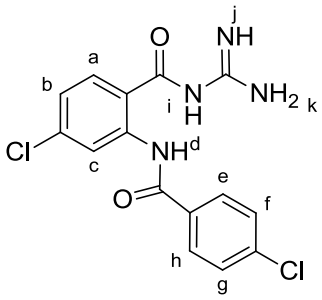
N-Amidino-2-benzoylamino-4-chlorobenzamide **(143b)** was synthesized from 7-chloro-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(127b)**. Its IR spectrum showed peaks at 3507, 3354 (N-H str.), 1658, 1641 (C=O str.), 1586 (N-H bend.) and 715 (C-Cl str.) cm^{-1}. Its ^{1}H NMR spectrum showed peaks at δ13.84 (*bs*, 1H, NH_j), 8.7960-8.8011 (*d*, 1H, ArH_c), 8.23-8.26 (*d*, 1H, ArH_a), 8.00-8.01 (*dd*, 2H, ArH_e & ArH_i), 7.84 (*bs*, 2H, NH_{2l}), 7.52-7.62 (*m*, 3H, ArH_f, ArH_g & ArH_h), 7.25 (*bs*, 1H, NH_d), 7.09-7.12 (*d*, 1H, ArH_b) and 6.98 (*bs*, 1H, NH_k). Its mass spectrum showed (M^+) and (M+2) at m/z 315.99 and 317.49 respectively.



(143b)



(144b)



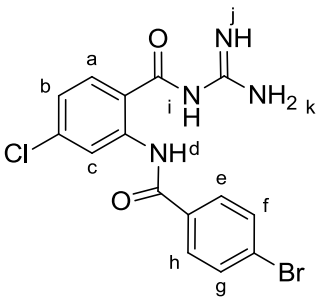
(145b)

Similarly, *N*-amidino-4-chloro-2-(4-methylbenzoylamino)benzamide **(144b)** was obtained from 7-chloro-2-*p*-tolyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(128b)**. Its IR spectrum showed peaks at 3379 (N-H str.), 1659 (C=O str.), 1584 (N-H bend.) and 743 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 13.70 (*bs*, 1H, NH_j), 8.7700-8.7742 (*d*, 1H, ArH_c), 8.21-8.24 (*d*, 1H, ArH_a), 7.88-7.90 (*dd*, 2H, ArH_e & ArH_i), 7.68-8.07 (*bs*, 2H, NH_{2l}), 7.33-7.35 (*dd*, 2H, ArH_f & ArH_h), 7.11-7.14 (*d*, 1H, ArH_b), 6.98 (*bs*, 1H, NH_k), 3.40 (*bs*, 1H, NH_d) and 2.39 (*s*, 3H, ArCH_{3g}). Its mass spectrum showed (M^+) and (M+2) at m/z 330.44 and 333.01 respectively.

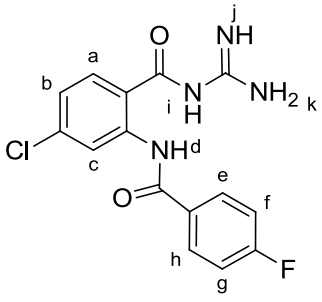
The compound (**145b**) was obtained from 7-chloro-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(129b)**. Its IR spectrum showed peaks at 3421 (N-H str.), 1660 (C=O str.), 1588 (N-H bend.) and 760 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 13.55 (*bs*, 1H, NH_i), 8.64 (*s*, 1H, ArH_c), 8.15-8.17 (*d*, 1H, ArH_a), 7.98-8.00 (*d*, 1H, ArH_e), 7.92-7.94 (*d*, 1H, ArH_h), 7.79 (*bs*, 2H, NH_{2k}), 7.67 (*bs*, 1H, NH_d), 7.56-7.60 (*dd*, 2H, ArH_f & ArH_g), 7.27-7.35 (*bs*,

1H, NH_j) and 7.13-7.15 (*d*, 1H, ArH_b). Its mass spectrum showed (M^+) and (M+2) at m/z 350.35 and 352.61 respectively.

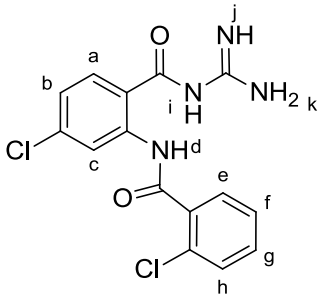
N-Amidino-2-(4-bromobenzoylamino)-4-chlorobenzamide **(146b)** was synthesized from 7-chloro-2-(4-bromophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(130b)**. Its IR spectrum showed peaks at 3099 (N-H str.), 1664 (C=O str.), 1591 (N-H bend.) and 867, 746 (C-Br & C-Cl str.) cm^{-1}. Its ^{1}H NMR spectrum showed peaks at δ13.91 (*bs*, 1H, NH_i), 8.73 (*s*, 1H, ArH_c), 8.19-8.21 (*d*, 1H, ArH_a), 7.88-7.91 (*d*, 1H, ArH_e), 7.69-7.71 (*d*, 1H, ArH_h), 7.29-8.06 (*bs*, 4H, NH_d, NH_j & NH_{2k}), 7.05-7.11 (*dd*, 2H, ArH_f & ArH_g) and 6.79-6.82 (*d*, 1H, ArH_b). Its mass spectrum showed (M^+) at m/z 393.99.



(146b)



(147b)

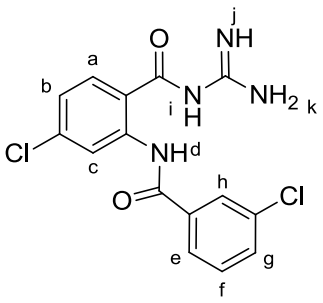


(148b)

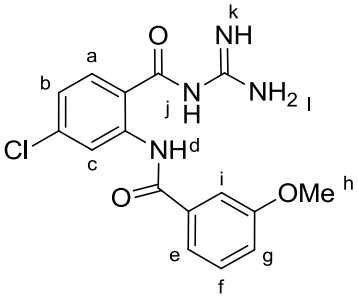
Similarly, *N*-amidino-4-chloro-2-(4-fluorobenzoylamino)benzamide **(147b)** was obtained from 7-chloro-2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(131b)**. Its infrared spectrum showed peaks at 3427 (N-H str.), 1662 (C=O str.), 1597 (N-H bend.), 1349 (C-F str.), 755 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 13.86 (*bs*, 1H, NH_i), 8.7542-8.7592 (*d*, 1H, ArH_c), 8.22-8.24 (*d*, 1H, ArH_a), 8.04-8.07 (*dd*, 2H, ArH_e & ArH_h), 7.87-8.95 (*bs*, 2H, NH_{2k}), 7.30-7.34 (*dd*, 2H, ArH_f & ArH_g), 7.10-7.13 (*d*, 1H, ArH_b), 7.03 (*bs*, 1H, NH_d) and 6.81 (*bs*, 1H, NH_j). Its mass spectrum showed (M^+) and (M+2) at m/z 334.74 and 336.22 respectively.

The compound (**148**) was obtained from 7-chloro-2-(2-chlorophenyl)-4*H*-benzo[*d*][1,3]-oxazin-4-one **(132b)**. Its infrared spectrum showed peaks at 3429 (N-H str.), 1667 (C=O str.), 1582 (N-H bend.) and 745 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 13.55 (*bs*, 1H, NH_i), 8.7214-8.7260 (*d*, 1H, ArH_c), 8.23-8.25 (*d*, 1H, ArH_a), 7.68-7.70 (*d*, 1H, ArH_h), 7.54-7.57 (*d*, 1H, ArH_e), 7.49-7.53 (*t*, 1H, ArH_f), 7.44-7.48 (*t*, 1H, ArH_g), 7.14-7.17 (*d*, 1H, ArH_b), 7.33-7.62 (*bs*, 2H, NH_{2k}) and 6.81-6.95 (*bs*, 2H, NH_d & NH_j). Its mass spectrum showed (M^+) and (M+2) at m/z 351.05 and 352.94 respectively.

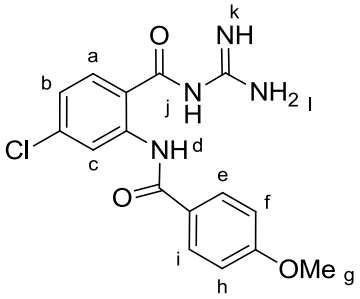
N-Amidino-4-chloro-2-(3-chlorobenzoylamino)benzamide **(149b)** was synthesized from 7-chloro-2-(3-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(133b)**. Its IR spectrum showed peaks at 3416, 3335 (N-H str.), 1641 (C=O str.), 1584 (N-H bend.), 734 (C-Cl str.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 13.97 (*bs*, 1H, NH_i), 8.74-8.97 (*m*, 2H, ArH_a & ArH_c), 8.48-8.52 (*d*, 1H, ArH_e), 7.93 (*s*, 1H, ArH_h), 7.12-6.60 (*m*, 3H, ArH_b, ArH_f & ArH_g) and 6.78-8.97 (*bs*, 4H, NH_d, NH_j & NH_{2k}). Its mass spectrum showed (M^+) and (M+2) at m/z 351.33 and 353.47 respectively.



(149b)



(150b)



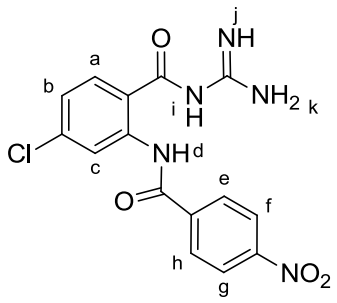
(151b)

Similarly, *N*-amidino-4-chloro-2-(3-methoxybenzoylamino)benzamide **(150b)** was obtained from 7-chloro-2-(3-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(134b)**. Its IR spectrum showed peaks at 3428 (N-H str.), 1662 (C=O str.), 1585 (N-H bend.), 740 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 13.82 (*bs*, 1H, NH_j), 8.7909-8.7960 (*d*, 1H, ArH_c), 8.25-8.27 (*d*, 1H, ArH_a), 7.80-7.90 (*bs*, 2H, NH_{2l}), 7.56-7.58 (*d*, 1H, ArH_g), 7.48 (*s*, 1H, ArH_i), 7.44-7.48 (*t*, 1H, ArH_f), 7.30-7.40 (*bs*, 1H, NH_d), 7.15-7.18 (*d*, 1H, ArH_e), 7.11-7.14 (*d*, 1H, ArH_b), 6.99 (*bs*, 1H, NH_k) and 3.85 (*s*, 3H, OCH_{3h}). Its mass spectrum showed (M^+) and (M+2) at m/z 334.74 and 336.22 respectively.

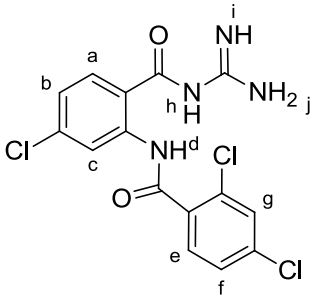
The compound (**151b**) was prepared from 7-chloro-2-(4-methoxyphenyl)-4*H*-benzo[*d*]-[1,3]oxazin-4-one **(135b)**. Its infrared spectrum showed peaks at 3380 (N-H str.), 1644 (C=O str.), 1582 (N-H bend.) and 760 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 13.63 (*bs*, 1H, NH_j), 8.66-8.67 (*d*, 1H, ArH_c), 8.17-8.20 (*d*, 1H, ArH_a), 7.95-8.00 (*bs*, 2H, NH_{2l}), 7.20-7.60 (*bs*, 1H, NH_d), 7.13 (*bs*, 1H, NH_k), 7.03-7.11 (*m*, 2H, ArH_e & ArH_i), 6.81-6.84 (*m*, 2H, ArH_f & ArH_h), 6.57-6.59 (*d*, 1H, ArH_b) and 3.85 (*s*, 3H, OCH_{3g}).

N-Amidino-4-chloro-2-(4-nitrobenzoylamino)benzamide **(152b)** was synthesized from 7-chloro-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(136b)**. Its IR spectrum showed peaks at

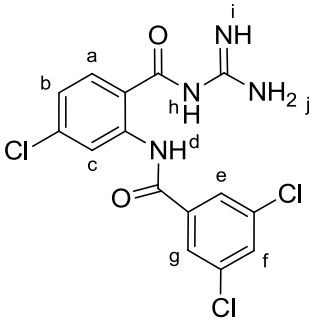
3393 (N-H str.), 1663, 1631 (C=O str.), 1591 (N-H bend.), 1538 and 1343 (NO_2), and 769 (C-Cl str.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 14.10 (*bs*, 1H, NH_i), 8.7100-8.7154 (*d*, 1H, ArH_c), 8.34-8.37 (*dd*, 2H, ArH_e & ArH_h), 8.18-8.22 (*m*, 3H, ArH_a, ArH_f & ArH_g), 7.88 (*bs*, 2H, NH_{2k}), 7.20-7.35 (*bs*, 1H, NH_d), 7.14-7.17 (*d*, 1H, ArH_b) and 6.79 (*bs*, 1H, NH_j). Its mass spectrum showed (M^+) and (M+2) at m/z 361.08 and 363.57 respectively.



(152b)



(153b)



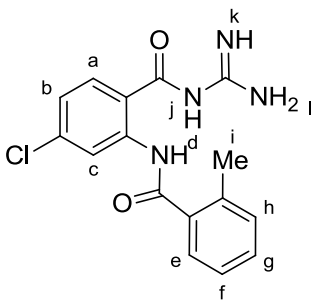
(154b)

Similarly, *N*-amidino-4-chloro-2-(2,4-dichlorobenzoylamino)benzamide **(153b)** was obtained from 7-chloro-2-(2,4-dichlorophenyl)-4*H*-benzo[*d*][1,3]-oxazin-4-one **(137b)**. Its IR spectrum showed peaks at 3438 (N-H str.), 1665 (C=O str.), 1582 (N-H str.) and 754 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 13.58 (*bs*, 1H, NH_h), 8.66-8.67 (*d*, 1H, ArH_c), 8.18-8.20 (*d*, 1H, ArH_a), 7.48-7.75 (*bs*, 2H, NH_{2j}), 7.70-7.72 (*d*, 1H, ArH_f), 7.6413-7.6462 (*d*, 1H, ArH_g), 7.49-7.51 (*d*, 1H, ArH_e), 7.13-7.16 (*d*, 1H, ArH_b), 7.00-7.10 (*bs*, 1H, NH_d) and 6.70-6.80 (*bs*, 1H, NH_i). Its mass spectrum showed (M^+) and (M+2) at m/z 385.76 and 387.01 respectively.

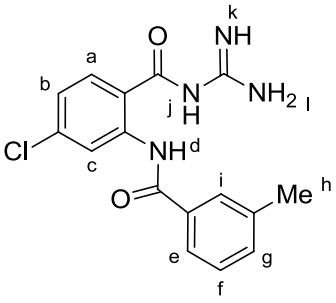
The compound (**154b**) was obtained from 7-chloro-2-(3,5-dichlorophenyl)-4*H*-benzo[*d*]-[1,3]oxazin-4-one **(138b)**. Its infrared spectrum showed peaks at 3570, 3397 (N-H str.), 1672 (C=O str.), 1600 (N-H bend.) and 712 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 14.61 (*bs*, 1H, NH_h), 9.03 (*s*, 1H, ArH_e), 9.0345 (*s*, 1H, ArH_f), 9.0444 (*s*, 1H, ArH_g), 8.77 (*s*, 1H, ArH_c), 8.18-8.21 (*d*, 1H, ArH_a), 7.98-8.01 (*bs*, 2H, NH_{2j}), 7.15-7.17 (*d*, 1H, ArH_b) and 7.07-7.08 (*bs*, 2H, NH_d & NH_i). Its mass spectrum showed (M^+) and (M+2) at m/z 384.22 and 386.94 respectively.

In the similar fashion, *N*-amidino-4-chloro-2-(2-methylbenzoylamino)benzamide **(155b)** was synthesized from 7-chloro-2-(2-*o*-tolyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(139b)**. Its IR spectrum showed peaks at 3405 (N-H str.), 1665 (C=O str.), 1585 (N-H bend.) and 730 (C-Cl str.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 13.77 (*bs*, 1H, NH_j), 8.78-8.79 (*d*, 1H, ArH_c),

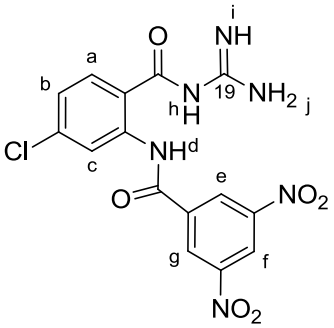
8.20-8.22 (*d*, 1H, ArH_a), 7.95-7.99 (*bs*, 2H, NH_{2l}), 7.78-7.85 (*dd*, 2H, ArH_e & ArH_h), 7.39-7.45 (*dd*, 2H, ArH_f & ArH_g), 7.10-7.13 (*d*, 1H, ArH_b), 7.05 (*bs*, 1H, NH_d), 6.81 (*bs*, 1H, NH_k) and 2.42 (*s*, 3H, ArCH_{3i}). Its mass spectrum showed (M^+) and (M+2) at m/z 330.92 and 332.75 respectively.



(155b)



(156b)



(157b)

Similarly, *N*-amidino-4-chloro-2-(3-methylbenzoylamino)benzamide **(156b)** was obtained from 7-chloro-2-(2-*m*-tolyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(140b)**. Its IR spectrum showed peaks at 3387 (N-H str.), 1653 (C=O str.), 1584 (N-H bend.) and 738 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 13.47 (*bs*, 1H, NH_j), 8.77-8.78 (*d*, 1H, ArH_c), 8.23-8.25 (*d*, 1H, ArH_a), 7.61-7.64 (*d*, 1H, ArH_e), 7.50-7.70 (*bs*, 1H, NH_{2l}), 7.38-7.43 (*t*, 1H, ArH_f), 7.33 (*s*, 1H, ArH_i), 7.30-7.32 (*d*, 1H, ArH_g), 7.10-7.13 (*d*, 1H, ArH_b), 6.85-7.07 (*bs*, 1H, NH_d), 6.81 (*bs*, 1H, NH_k) and 2.48 (*s*, 3H, ArCH_{3h}). Its mass spectrum showed (M^+) and (M+2) at m/z 330.51 and 332.50 respectively.

The compound (**157b**) with 3,5-dinitrophenyl group was obtained from 7-chloro-2-(3,5-dinitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(141b)**. Its infrared spectrum showed peaks at 3399 (N-H str.), 1673 (C=O str.), 1584 (N-H bend.), 1546 and 1354 (NO_2), and 730 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 14.61 (*bs*, 1H, NH_h), 9.04 (*s*, 1H, ArH_e), 9.03 (*s*, 1H, ArH_f), 8.99 (*s*, 1H, ArH_g), 8.73-8.74 (*d*, 1H, ArH_c), 8.17-8.19 (*d*, 1H, ArH_a), 7.95-8.10 (*bs*, 2H, NH_{2j}), 7.16-7.19 (*d*, 1H, ArH_b) and 6.90-7.10 (*bs*, 2H, NH_d & NH_i). Its mass spectrum showed (M^+) and (M+2) at m/z 407.81 and 408.67 respectively.

4.1.6. Synthesis of 2-substituted 4-chloro-*N*-pyridin-2-ylbenzamide derivatives (159-173)

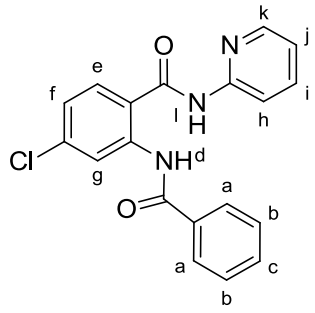
A series of 2-substituted 4-chloro-*N*-pyridin-2-yl-benzamides **(159-173)** was prepared from differently substituted 7-chloro-2-substituted-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones (**127a-**

141a) and neat 2-aminopyridine **(158)** as per **Scheme-IX**. After aqueous workup the solid obtained was recrystallized from methanol to afford the desired 2-substituted 4-chloro-*N*-pyridin-2-ylbenzamides **(159-173)**. All of these compounds were confirmed by their IR, ^{1}H NMR, elemental analysis and mass spectra.

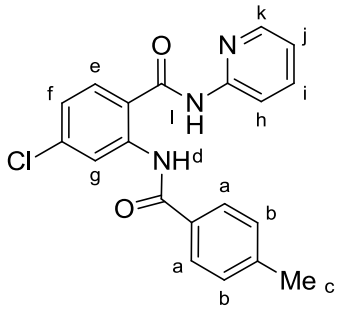
All of them showed characteristic vibrations at about 3300-3500 cm^{-1} for the NH stretching, 1550-1640 cm^{-1} for the NH bending and also halo stretching at around 750 cm^{-1}. All of the compounds were initially confirmed by absence of lactone carbonyl stretching in their respective IR spectra.

2-Benzoylamino-4-chloro-*N*-pyridin-2-ylbenzamide **(159)** was synthesized from 7-chloro-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(127b)**. Its IR spectrum showed peaks at 3323 (N-H str.), 1664, 1650 (C=O str.), 1600 (N-H bend.) and 783 (C-Cl str.) cm^{-1}. Its ^{1}H NMR spectrum showed peaks at δ 12.04 (*bs*, 1H, N*H*$_l$), 11.05 (*bs*, 1H, N*H*$_d$), 8.7328-8.7382 (*d*, 1H, Ar*H*$_g$), 8.38-8.40 (*d*, 1H, Ar*H*$_k$), 8.14-8.16 (*d*, 1H, Ar*H*$_h$), 8.06-8.08 (*d*, 1H, Ar*H*$_e$), 7.94-7.96 (*m*, 2H, Ar*H*$_a$), 7.80-7.85 (*t*, 1H, Ar*H*$_c$), 7.53-7.61 (*m*, 3H, Ar*H*$_b$ and Ar*H*$_j$), 7.21-7.24 (*dd*, 1H, Ar*H*$_f$) and 7.15-7.18 (*t*, 1H, Ar*H*$_i$). Its mass spectrum showed (M$^+$) and (M+2) at m/z 352.2 and 354.2 respectively.

Similarly, 4-chloro-2-(4-methylbenzoylamino)-*N*-pyridin-2-ylbenzamide **(160)** was obtained from 7-chloro-2-*p*-tolyl-4*H*-benzo[*d*][1,3]oxazin-4-one **(128b)**. Its IR spectrum showed peaks at 3322 (N-H str.), 1652 (C=O str.), 1597 (N-H bend.) and 784 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 12.02 (*bs*, 1H, N*H*$_l$), 11.02 (*bs*, 1H, N*H*$_d$), 8.74-8.75 (*d*, 1H, Ar*H*$_g$), 8.38-8.40 (*d*, 1H, Ar*H*$_k$), 8.14-8.16 (*d*, 1H , Ar*H*$_h$), 8.06-8.08 (*d*, 1H, Ar*H*$_e$), 7.80-7.85 (*m*, 3H, Ar*H*$_b$ and Ar*H*$_j$), 7.33-7.35 (*d*, 2H, Ar*H*$_a$), 7.19-7.21 (*dd*, 1H, Ar*H*$_f$), 7.15-7.18 (*t*, 1H, Ar*H*$_i$) and 2.41 (*s*, 3H, ArC*H*$_{3c}$). Its mass spectrum showed (M$^+$) and (M+2) at m/z 366.2 and 368.2 respectively.



(159)



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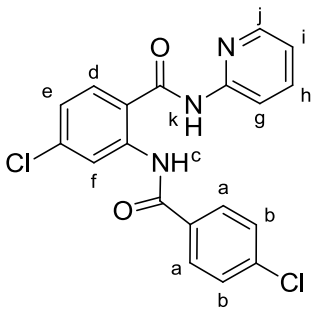
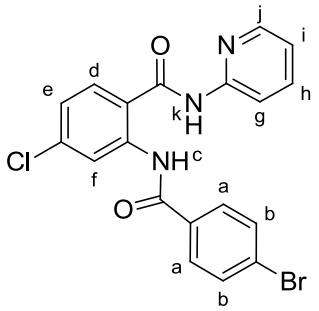


(161)

The compound 4-chloro-2-(4-chlorobenzoylamino)-*N*-pyridin-2-ylbenzamide **(161)** was obtained from 7-chloro-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(129b)**. Its infrared spectrum showed peaks at 3335 (N-H str.), 1654 (C=O str.), 1599 (N-H bend.) and 784 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 11.89 (*bs*, 1H, NH_k), 11.08 (*bs*, 1H, NH_c), 8.59-8.60 (*d*, 1H, ArH_f), 8.38-8.40 (*d*, 1H, ArH_j), 8.10-8.12 (*d*, 1H, ArH_g), 8.03-8.05 (*d*, 1H, ArH_d), 7.91-7.95 (*d*, 2H, ArH_b), 7.81-7.86-5 (*t*, 1H, ArH_i), 7.58-7.62 (*d*, 2H, ArH_a), 7.25-7.28 (*dd*, 1H, ArH_e) and 7.16-7.19 (*t*, 1H, ArH_h). Its mass spectrum showed (M^+) and (M+2) at m/z 386.2 and 388.1 respectively.

Similarly, 2-(4-bromobenzoylamino)-4-chloro-*N*-pyridin-2-ylbenzamide **(162)** was synthesized from 7-chloro-2-(4-bromophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(130b)**. Its IR spectrum showed peaks at 3350 (N-H str.), 1652 (C=O str.), 1576 (N-H bend.) and 783 (C-Cl str.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 12.04 (*bs*, 1H, NH_k), 11.05 (*bs*, 1H, NH_c), 8.6643-8.6683 (*d*, 1H, ArH_f), 8.38-8.39 (*d*, 1H, ArH_j), 8.06-8.15 (*d*, 2H, ArH_b), 7.92-7.94 (*d*, 1H, ArH_g), 7.85-7.87 (*d*, 1H, ArH_d), 7.69-7.74 (*d*, 2H, ArH_a), 7.22-7.24 (*dd*, 2H, ArH_e) and 7.15-7.18 (*t*, 1H, ArH_h). Its mass spectrum showed (M^+) and (M+2) at m/z 430.34 and 432.29 respectively.

Similarly, 4-chloro-2-(4-fluorobenzoylamino)-*N*-pyridin-2-ylbenzamide **(163)** was obtained from 7-chloro-2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(131b)**. Its IR spectrum showed peaks at 3350 (N-H str.), 1659 (C=O str.), 1599 (N-H bend.), 1402 (C-F str.) and 782 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 13.58 (*bs*, 1H, NH_k), 11.99 (*bs*, 1H, NH_c), 8.82-8.83 (*d*, 1H, ArH_f), 8.08-8.10 (*d*, 1H, ArH_g), 8.04-8.06 (*d*, 2H , ArH_b), 7.88-7.89 (*d*, 1H, ArH_j), 7.54-7.58 (*t*, 1H, ArH_i), 7.29-7.35 (*m*, 2H, ArH_a), 7.11-7.13 (*dd*, 1H, ArH_e), 6.68-6.70 (*d*, 1H, ArH_d) and 6.60-6.63 (*t*, 1H, ArH_h). Its mass spectrum showed (M^+) and (M+2) at m/z 368.1 and 370 respectively.



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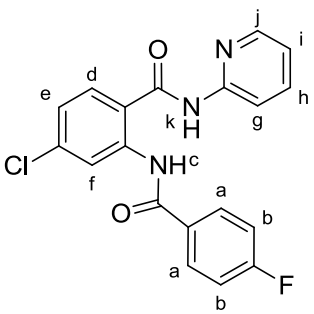
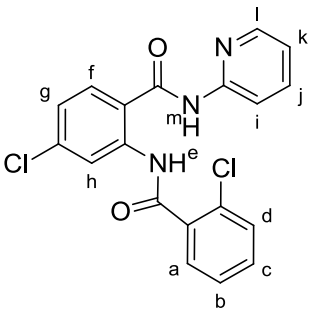


(163)

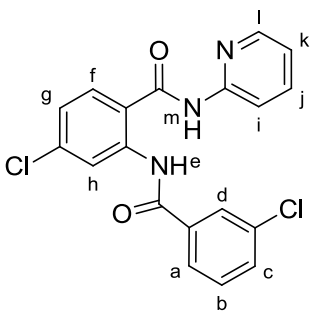


(164)

The compound 4-chloro-2-(2-chlorobenzoylamino)-*N*-pyridin-2-ylbenzamide **(164)** was obtained from 7-chloro-2-(2-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(132b)**. Its infrared spectrum showed peaks at 3420 (N-H str.), 1663 (C=O str.), 1598 (N-H bend.) and 781 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 11.37 (*bs*, 1H, NH_m), 10.91 (*bs*, 1H, NH_e), 8.52 (*s*, 1H, ArH_h), 8.32-8.33 (*d*, 1H, ArH_l), 8.02-8.04 (*d*, 1H, ArH_i), 7.95-7.97 (*d*, 1H, ArH_f), 7.70-7.74 (*t*, 1H, ArH_b), 7.61-7.63 (*d*, 1H, ArH_d), 7.38-7.49 (*m*, 3H, ArH_a, ArH_c and ArH_k), 7.21-7.23 (*dd*, 1H, ArH_g) and 7.07-7.10 (*t*, 1H, ArH_j). Its mass spectrum showed (M^+) and (M+2) at m/z 386.2 and 388.2 respectively.

In a similar manner,4-chloro-2-(3-chlorobenzoylamino)-*N*-pyridin-2-ylbenzamide **(165)** was synthesized from 7-chloro-2-(3-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(133b)**. Its IR spectrum showed peaks at 3120 (N-H str.), 1669 (C=O str.), 1582 (N-H bend.) and 728 (C-Cl str.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 13.78 (*bs*, 1H, NH_m), 11.05 (*bs*, 1H, NH_e), 8.8226-8.8279 (*d*, 1H, ArH_h), 8.6632-8.6686 (*d*, 1H, ArH_d), 8.37-8.39 (*d*, 1H, ArH_l), 8.14-8.16 (*d*, 1H, ArH_i), 8.12-8.13 (*d*, 1H, ArH_f), 7.84-7.87 (*m*, 2H, ArH_a), 7.79-7.83 (*t*, 1H, ArH_k), 7.62-7.66 (*t*, 1H, ArH_b), 7.21-7.23 (*dd*, 1H, ArH_g), 7.14-7.17 (*t*, 1H, ArH_j) and 7.09-7.11 (*dd*, 1H, ArH_c). Its mass spectrum showed (M^+) and (M+2) at m/z 386.19 and 388.30 respectively.

Similarly, 4-chloro-2-(3-methoxybenzoylamino)-*N*-pyridin-2-ylbenzamide **(166)** was obtained from 7-chloro-2-(3-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(134b)**. Its IR spectrum showed peaks at 3118 (N-H str.), 1642 (C=O str.), 1575 (N-H bend.) and 774 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 12.12 (*bs*, 1H, NH_n), 11.17 (*bs*, 1H, NH_f), 8.79-8.80 (*d*, 1H, ArH_i), 8.48-8.49 (*d*, 1H, ArH_e), 8.35-8.37 (*d*, 1H, ArH_m), 8.08-8.10 (*d*, 1H, ArH_j), 8.03-8.05 (*d*, 1H, ArH_c), 7.92-7.94 (*d*, 1H, ArH_g), 7.47-7.53 (*m*, 2H, ArH_a & ArH_l), 7.40-7.44 (*t*, 1H, ArH_b), 7.27-7.29 (*dd*, 1H, ArH_h), 7.15-7.19 (*t*, 1H, ArH_k) and 3.87 (*s*, 3H, OCH_{3d}). Its mass spectrum showed (M^+) and (M+2) at m/z 381.21 and 383 respectively.



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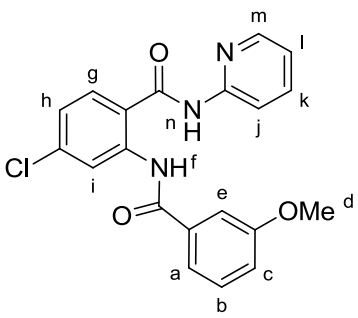

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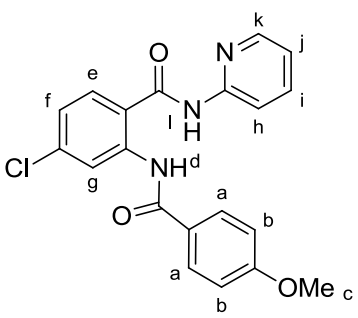
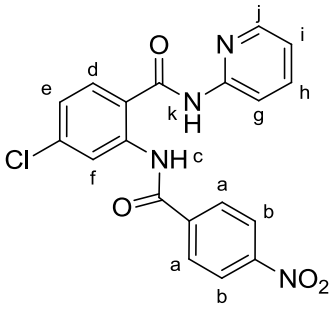


(167)

The compound 4-chloro-2-(4-methoxybenzoylamino)-*N*-pyridin-2-ylbenzamide **(167)** was obtained from 7-chloro-2-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(135b)**. Its IR spectrum showed peaks at 3332 (N-H str.), 1652 (C=O str.), 1575 (N-H bend.) and 780 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 12.00 (*bs*, 1H, NH_l), 11.01 (*bs*, 1H, NH_d), 8.7526-8.7580 (*d*, 1H, ArH_g), 8.38-8.40 (*d*, 1H, ArH_k), 8.15-8.17 (*d*, 1H, ArH_h), 8.05-8.07 (*d*, 1H, ArH_e), 7.90-7.93 (*dd*, 2H, ArH_b), 7.81-7.85 (*d*, 1H, ArH_j), 7.18-7.20 (*dd*, 1H, ArH_f), 7.15-7.17 (*t*, 1H, ArH_i), 7.04-7.06 (*dd*, 1H, ArH_a) and 3.86 (*s*, 3H, OCH_{3c}).

In a similar fashion, 4-chloro-2-(4-nitrobenzoylamino)-*N*-pyridin-2-ylbenzamide **(168)** was synthesized from 7-chloro-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(136b)**. Its IR spectrum showed peaks at 3350 (N-H str.), 1658 (C=O str.), 1576 (N-H bend.), 1517 and 1345 (NO_2), and 782 (C-Cl str.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 12.11 (*bs*, 1H, NH_k), 11.09 (*bs*, 1H, NH_c), 8.5829-8.5882 (*d*, 1H, ArH_f), 8.35-8.37 (*d*, 1H, ArH_j), 8.34-8.35 (*dd*, 2H, ArH_b), 8.13-8.16 (*dd*, 1H, ArH_g), 8.09-8.12 (*dd*, 2H, ArH_a), 8.04-8.06 (*d*, 1H, ArH_d), 7.78-7.83 (*t*, 1H, ArH_i), 7.23-7.26 (*dd*, 1H, ArH_e) and 7.13-7.17 (*t*, 1H, ArH_h). Its mass spectrum showed (M^+) and (M+2) at m/z 397.2 and 399.3 respectively.

Similarly, 4-chloro-2-(2,4-dichlorobenzoylamino)-*N*-pyridin-2-ylbenzamide **(169)** was obtained from 7-chloro-2-(2,4-dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(137b)**. Its IR spectrum showed peaks at 3328 (N-H str.), 1675, 1654 (C=O str.), 1575 (N-H bend.) and 783 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 11.45 (*bs*, 1H, NH_l), 10.90 (*bs*, 1H, NH_d), 8.5221-8.5265 (*d*, 1H, ArH_g), 8.31-8.33 (*d*, 1H, ArH_k), 8.01-8.03 (*d*, 1H, ArH_h), 7.95-7.99 (*dd*, 2H, ArH_a), 7.70-7.74 (*t*, 1H, ArH_j), 7.61-7.63 (*d*, 1H, ArH_e), 7.5137-7.5185 (*d*, 1H, ArH_c), 7.39-7.42 (*dd*, 1H, ArH_b), 7.18-7.21 (*dd*, 1H, ArH_f) and 7.07-7.10 (*t*, 1H, ArH_i). Its mass spectrum showed (M^+) and (M+2) at m/z 420.1 and 422 respectively.



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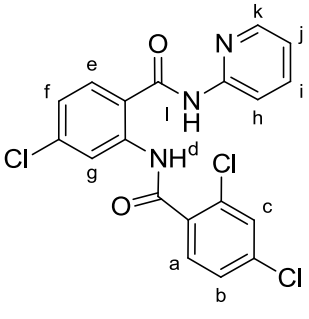
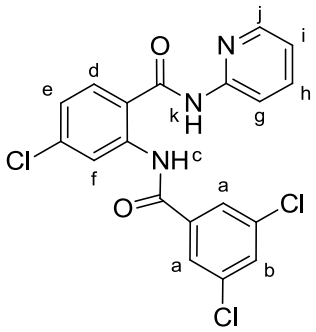


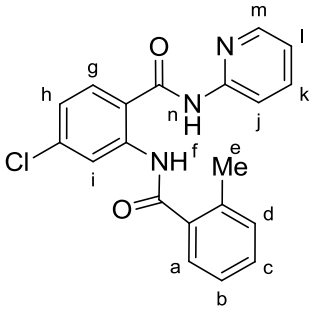
(169)



(170)

The compound 4-chloro-2-(3,5-dichlorobenzoylamino)-*N*-pyridin-2-ylbenzamide **(170)** was obtained from 7-chloro-2-(3,5-dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(138b)**. Its infrared spectrum showed peaks at 3408 (N-H str.), 1680, 1655 (C=O str.), 1680 (N-H bend.) and 779 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 12.11 (*bs*, 1H, NH_k), 11.00 (*bs*, 1H, NH_c), 9.1246-9.1294 (*d*, 2H, ArH_a), 9.0829-9.0878 (*t*, 1H, ArH_b), 8.35-8.36 (*d*, 1H, ArH_f), 8.34-8.35 (*d*, 1H, ArH_j), 8.17-8.19 (*d*, 2H, ArH_g), 8.02-8.04 (*d*, 1H, ArH_d), 7.77-7.82 (*t*, 1H, ArH_i), 7.30-7.33 (*dd*, 1H, ArH_e) and 7.12-7.15 (*t*, 1H, ArH_h). Its mass spectrum showed (M^+), (M+2) and (M+4) at m/z 420.3, 422.1 and 424.2 respectively.

In the similar way, 4-chloro-2-(2-methylbenzoylamino)-*N*-pyridin-2-ylbenzamide **(171)** was synthesized from 7-chloro-2-(2-*o*-tolyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(139b)**. Its IR spectrum showed peaks at 3320 (N-H str.), 1653 (C=O str.), 1574 (N-H bend.) and 781 (C-Cl str.) cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 11.41 (*bs*, 1H, NH_n), 10.88 (*bs*, 1H, NH_f), 8.6616-8.6667 (*d*, 1H, ArH_i), 8.35-8.37 (*d*, 1H, ArH_m), 8.06-8.08 (*d*, 1H, ArH_j), 8.00-8.02 (*d*, 1H, ArH_g), 7.73-7.76 (*t*, 1H, ArH_b), 7.56-7.58 (*d*, 1H, ArH_d), 7.37-7.41 (*t*, 1H, ArH_a), 7.27-7.31 (*t*, 2H, ArH_c & ArH_l), 7.19-7.22 (*dd*, 1H, ArH_h), 7.10-7.13 (*t*, 1H, ArH_k) and 2.48 (*s*, 3H, ArCH_{3e}). Its mass spectrum showed (M^+) and (M+2) at m/z 366.2 and 368.2 respectively.



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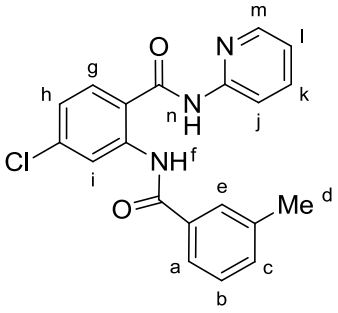
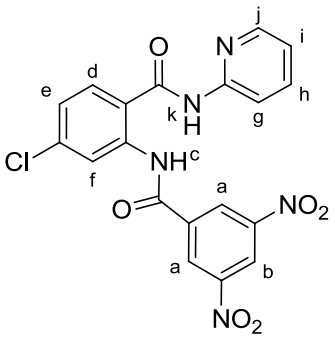


(172)



(173)

Similarly, 4-chloro-2-(3-methylbenzoylamino)-*N*-pyridin-2-ylbenzamide **(172)** was obtained from 7-chloro-2-(2-*m*-tolyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(140b)**. Its IR spectrum showed peaks at 3363 (N-H str.), 1651 (C=O str.), 1574 (N-H bend.) and 778 (C-Cl str.) cm^{-1}. Its ^1H NMR showed peaks at δ 12.04 (*bs*, 1H, NH_n), 10.92 (*bs*, 1H, NH_f), 8.76-8.77 (*d*, 1H, ArH_i), 8.37-8.38 (*d*, 1H, ArH_m), 8.16-8.18 (*d*, 1H, ArH_j), 8.06-8.08 (*d*, 1H, ArH_g), 7.78-7.83 (*t*, 1H, ArH_b), 7.77 (*s*, 1H, ArH_e), 7.72-7.74 (*d*, 1H, ArH_c), 7.42-7.44 (*d*, 1H, ArH_a), 7.38-7.42 (*t*, 1H,

ArH_l), 7.17-7.20 (*dd*, 1H, ArH_h), 7.13-7.16 (*t*, 1H, ArH_k) and 2.43 (*s*, 3H, ArCH_{3d}). Its mass spectrum showed (M^+) and (M+2) at m/z 366.2 and 368.2 respectively.

The compound 4-chloro-2-(3,5-dinitrobenzoylamino)-*N*-pyridin-2-ylbenzamide **(173)** was obtained from 7-chloro-2-(3,5-dinitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **(140b)**. Its infrared spectrum showed peaks at 3408 (N-H str.), 1679, 1654 (C=O str.), 1585 (N-H bend.), 1521 and 1345 (NO_2), and 778 (C-Cl str.) cm^{-1}. Its ^{1}H NMR showed peaks at δ 12.32 (*bs*, 1H, NH_k), 10.95 (*bs*, 1H, NH_c), 9.15-9.16 (*d*, 2H, ArH_a), 8.4705-8.4756 (*d*, 1H, ArH_f), 8.36-8.37 (*d*, 1H, ArH_j), 8.20-8.22 (*d*, 1H, ArH_g), 8.06-8.08 (*d*, 1H, ArH_d), 7.97 (*s*, 1H, ArH_b), 7.78-7.82 (*t*, 1H, ArH_i), 7.28-7.31 (*dd*, 1H, ArH_e) and 7.12-7.15 (*t*, 1H, ArH_h). Its mass spectrum showed (M^+) and (M+2) at m/z 442.2 and 444.2 respectively.

4.2. Biological studies

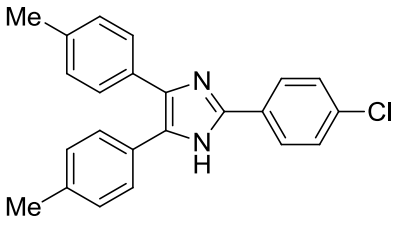
All the three series of synthesized compounds were evaluated for their *in vitro* platelet aggregation inhibitory activity and the results of these studies are summarized in below mentioned tables. One series of triazino derivatives was extensively studied further for *ex vivo* and *in vivo* activities.

4.2.1. Biological evaluation of 2-substituted 4,5-diaryl-1*H*-imidazoles (52a-68a and 52b-68b)

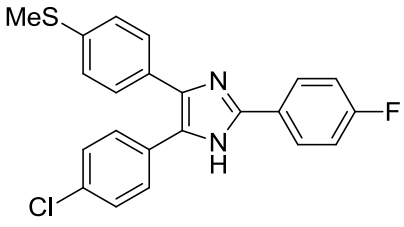
4.2.1.1. Human *in vitro* Platelet Aggregation Assay

The newly synthesized compounds were screened for their *in vitro* platelet aggregation inhibitory activity on whole human blood.[11] The study was performed using Whole Blood Aggregometer, Chronolog Corporation, Haverton, PA, USA. The inhibitory activity of compounds **(52a-68a** and **52b-68b)** was measured and compared with inhibition induced by standard drug Aspirin (10 μg/ml) (**Table 1**). Each assay was performed three times, taking control and aspirin as a standard for comparative assay each time. Whole blood aggregometer measures inhibition of platelet aggregation induced by ADP (10 μM) in ohms which is the resistance produced by accumulation of aggregates on the electrode. The control or normal platelet aggregation was found to be having a reading of 12.2 ± 1.92 Ω and for aspirin (10 μg/ml) the reading was 7.5 ± 1.21 Ω (38.52 % inhibition of aggregation). The standard range of readings for inhibition of ADP (10 μM) induced aggregation for aspirin is 6-24 Ω.

From the *in vitro* evaluation (**Table 1**) of the test compounds (**52a-68a**) bearing 4-chlorophenyl group, eleven compounds were found to have prominent activity. Compounds (**53a**, **54a**, **61a** and **65a**) produced more than 60 % inhibition while compounds (**52a**, **55a**, **56a**, **57a**, **62a**, **66a** and **67a**) were found to be comparable in activity with aspirin. Out of these compounds, (**65a**) was the most potent (76.2 %), being twice as potent as aspirin.



(**65a**)



(**62b**)

In the series of compounds bearing 4-fluoropenyl group (**52b-68b**), ten compounds were found to be more active than the standard drug aspirin at the same dose. Among these compounds, compounds (**54b**, **55b**, **57b-63b** and **65b**) were found to be more potent or of comparable potency to aspirin showing more than 40 % inhibition of platelet aggregation *in vitro*. The compound (**62b**) showed the highest inhibition (83.6 %).

Table 1: *In vitro* Platelet Aggregation Assay of 2-substituted 4,5-diaryl-1H-imidazole derivatives (**52a-68a** and **52b-68b**)

Comp	% Inhibition	Comp	% Inhibition
52a	**49.18**	**52b**	17.21
53a	**66.39**	**53b**	4.91
54a	**66.39**	**54b**	**53.03**
55a	**59.02**	**55b**	**45.90**
56a	**47.54**	**56b**	36.06
57a	**52.45**	**57b**	**48.36**
58a	1.63	**58b**	**54.91**
59a	21.31	**59b**	**43.44**
60a	9.02	**60b**	**43.44**
61a	**60.65**	**61b**	**68.85**
62a	**47.54**	**62b**	**83.60**
63a	36.88	**63b**	**49.18**
64a	13.93	**64b**	27.04
65a	**76.22**	**65b**	**68.03**
66a	42.62	**66b**	10.65
67a	42.62	**67b**	19.67
68a	27.04	**68b**	23.77
-	**-**	**Aspirin**	38.52

4.2.2. Biological evaluation of 5,6-diaryl-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amines (94-110)

The newly synthesized compounds were studied for their *in vitro* platelet aggregation inhibitory activity. Our earlier study has shown that this type of compounds do not exhibit any cytotoxicity rather they show protective role in malondialdehyde (MDA), catalase and intracellular reactive oxygen species (ROS) generation assays. The whole human blood aggregation study was done as per the above described procedure. Each reading was taken in

triplicate for the test samples, using control and a standard drug aspirin for comparative reading each time. The percent inhibition of platelet aggregation was determined for each test sample in comparison to the control and the standard aspirin. The inhibitory values were calculated accordingly as shown in **Table 2**.

4.2.2.1. Human *in vitro* Platelet Aggregation Assay

From the *in vitro* evaluation (**Table 2**) of the test compounds (**94-110**), ten compounds were found to have prominent activity. Compounds (**94**, **97, 101-105, 107**, **108** and **110**) produced more than 60 % inhibition while compounds (**95**, **96**, **99**, **100**, **106** and **109**) were found to be comparable in activity with aspirin. Out of these compounds, (**105**) was the most potent, being twice as potent as aspirin.

4.2.2.2. *Ex vivo* platelet aggregation study

Almost all of the compounds in 5,6-diaryl-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amine series showed good to moderate inhibition of platelet aggregation in the *in vitro* study. Hence, all the compounds were screened further for their *ex vivo* platelet aggregation inhibition. The whole blood aggregation method was used for this purpose in which blood was withdrawn from animals, 2 hrs after pretreatment of the group with test samples by oral dosing, along with the control group and aspirin treated group (**Table 2**).

From the *ex vivo* study of the tested compounds (**94-110**), six compounds (**103**, **105**, **95**, **106**, **108** and **109**) were found with noticeable activity. Out of these five compounds, **105** again was found to be the most potent (53.19 % inhibition), which was almost double the activity of aspirin. Compounds (**95, 103, 106, 108** and **109**) produced comparable inhibition of platelet aggregation to aspirin. Even though these compounds were found to be less potent in comparison to another standard drug clopidogrel which acted through a different mechanism of action ($P2Y_{12}$ inhibition), their potential vasodilatory effect could give them an additional advantage.

4.2.2.3. *In vivo* antithrombotic study

a) Ferric chloride induced thrombosis

All the synthesized compounds were evaluated for their antithrombotic activity using $FeCl_3$ induced thrombosis model, as reported earlier.[12] From **Table 2**, it could be seen that almost all the compounds (**94-110**) inhibited the thrombus formation as evidenced from their

respective thrombus weight after treatment at a dose of 10 mg/kg *p.o.* Compounds (**97, 98, 101, 102** and **105**) decreased the thrombus weight significantly as compared to the standard drug and the control. Two compounds (**101** and **105**) showed noteworthy efficacy in this model. The time to occlusion (TTO) was also measured as a parameter indicating obstruction to blood flow after formation of clot/thrombus. Increase in TTO was considered as a preventive measure for prolongation of thrombus formation. Compounds (**97**, **102**,**104**, **105**, **107** and **110**) significantly increased TTO as compared to the standard drug and the control (**Table 2**).

Table 2: *In vitro, ex vivo* and *in vivo* platelet aggregation activity of 5,6-diaryl-*N*-(2-morpholinoethyl)-1,2,4-triazin-3-amines **(94-110)**

Comp.	% Inhibition of Platelet aggregation		Thrombus wt (mg)	% Inhibition of thrombosis	Time to Occlusion (min)	Bleeding Time (min)
	In vitro	*Ex Vivo*				
Control	-	-	6.60	-	15.0	18.0
94	**68.88**	22.37	4.90	25.75	12.5	24.0
95	48.02	**44.47**	5.00	24.24	12.0	17.5
96	39.51	23.82	4.90	25.75	20.5	18.0
97	**68.72**	19.94	4.20	36.36	29.0	24.5
98	34.79	32.53	4.20	36.36	18.0	16.0
99	36.29	26.17	4.50	31.81	23.5	19.5
100	46.77	35.58	4.25	35.60	21.5	16.5
101	**71.25**	19.87	**4.00**	**39.39**	21.0	19.5
102	**62.50**	18.58	4.10	37.87	27.5	>30
103	**63.95**	**37.65**	4.80	27.27	12.5	17.0
104	**66.93**	19.11	4.30	34.84	27.0	25.5
105	**75.00**	**53.19**	**4.00**	**39.39**	**>30**	**25.0**
106	41.93	**36.47**	4.85	26.51	21.5	20.5
107	**70.16**	17.64	4.25	35.60	29.5	25.0
108	**58.79**	**45.29**	4.75	28.03	19.0	20.5
109	49.68	**36.42**	4.25	35.60	21.0	16.5
110	**58.87**	17.64	4.00	39.39	27.0	>30
Clopidogrel[a]	-	84.03	3.00	54.54	>30	>30
Aspirin[b]	34.00	47.80	3.00	54.54	>30	>30

[a]: Clopidogrel used at a dose of 25 mg/kg body weight; [b]: Aspirin used at a dose of 50 mg/kg body weight.

b) Arterio-venous (AV) shunt thrombosis

Further, to ensure antithrombotic efficacy of the compound (**105**), it was evaluated by previously known AV shunt model.[13] No temperature fall was observed upto 20 min which

showed the non-occlusive response indicating the potential antithrombotic action of compound (**105**).

c) Bleeding time

Bleeding time was used as a parameter to evaluate the hemorrhagic properties of antithrombotic drugs. Hence, tail bleeding method[14] was used at a dose of 10 mg/kg of body weight for the test samples. Compounds (**97** and **104-107**) showed increased but significantly lower bleeding time than standard drugs clopidogrel and aspirin. The optimum increase in bleeding time by these compounds could be of great advantage since that would overcome the fatal bleeding complications (**Table 2**).

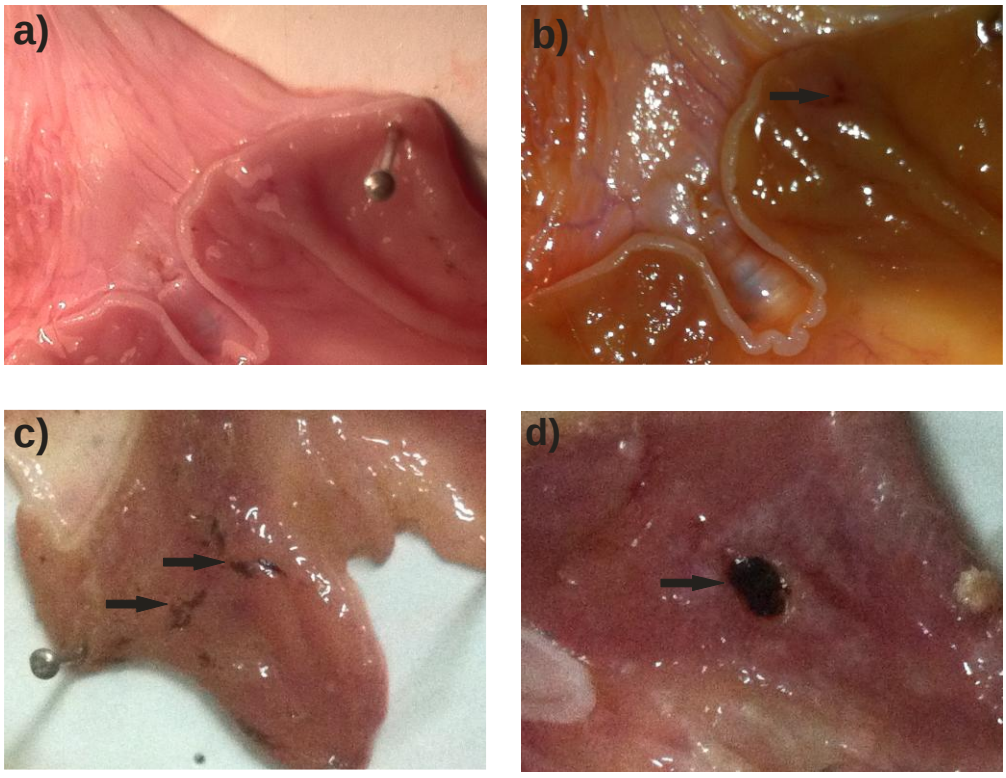


Fig. 4: Effect of compound (**105**) and aspirin on gastric mucosa **a)** Control with no gastric lesions; **b)** Compound (**105**) showing mild gastric lesions (10 mg/kg); **c)** Compound (**105**) showing moderate gastric lesions (100 mg/kg); **d)** Aspirin showing severe gastric lesions (100 mg/kg).

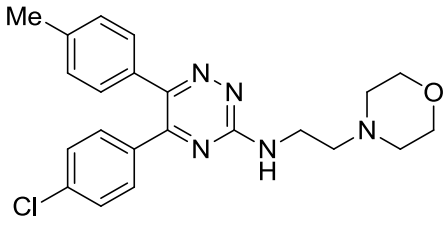
d) Gastric ulceration

The gastric ulceration model[15] was selected to ascertain the undesired side effects, if any, of the test sample (**105**). The results suggested that, there was no gastric ulceration in the control (**Fig. 4a**) while a mild ulceration was observed after 10 mg/kg dose (**Fig. 4b**) of the test compound (**105**), whereas moderate ulceration was observed at 100 mg/kg dose (**Fig. 4c**). Still,

at 100 mg/kg dose the ulceration was much less than the standard drug aspirin which caused severe ulceration at the same dose (100 mg/kg) (**Fig. 4d**).

The effect of various groups on the basic 5,6-diaryl-1,2,4-triazine scaffold was studied with respect to antiplatelet activity of the synthesized compounds. Among the compounds in the series, compound (**105**) was found to be the most potent inhibitor of *in vitro* platelet aggregation. This suggests that in the present series, *p*-methyl substituent on the 6-aryl ring and *p*-Cl substituent on the 5-aryl ring favor antiplatelet activity. While compound (**105**) showed the most prominent activity, its positional isomer (**95**) with *p*-methyl substituent on the 5-aryl ring and *p*-Cl substituent on the 6-aryl ring showed almost half the activity of compound (**105**). *p*-Halo substituent on the 5-aryl ring showed good activity in almost all of the compounds except for compound (**98**). Halo substitution at these positions increases the lipophilic character of the molecule. This could be one of the reasons for higher *in vitro* activity of *p*-halo substituted compounds at the 5-aryl ring. Compounds without halogens on both of the aryl rings showed overall decreased activity (**100** and **109**). Compounds with *m*-Cl substituent on the 5-aryl ring showed lower activity than the *p*-Cl substituted derivatives (compound **110** versus compound **105**). The compound (**96**) with *p*-Br substituent on the 5-aryl ring showed a drastic reduction in the activity whereas *p*-F substituent on this position retained the activity (**94** and **97**). Surprisingly, a compound (**98**) with *p*-Cl substituent on both the aryl rings has shown diminished activity while *p*-methyl substituents on both the aryl rings retained the same level of activity as shown by compound (**101**). In case of *ex vivo* activity of the synthesized compounds, five of the compounds (**95**, **98**, **105**, **106** and **108**) showed better activity than the rest. Compound (**105**) again emerged as the most potent compound with 53.19 % inhibition of platelet aggregation *ex vivo*. In case of bleeding time, compound (**98**) with *p*-Cl substituent on both of the aryl rings showed the least bleeding time which was unexpectedly low. Compound (**105**) showed the maximum bleeding time of 25 min in the series, in contrast to the reference drugs aspirin and clopidogrel which exhibited still higher bleeding times (430 min). The increased bleeding time after treatment by the current drugs is considered to be the main drawback, which causes fatal bleeding and loss of preventive mechanism of hemostasis. Hence, compounds with optimum bleeding time, such as **105**, would be beneficial for antiplatelet/antithrombotic therapy. Thrombus formation is one of the major causes of the thromboembolic diseases. To evaluate the antithrombotic efficacy of the tested compounds, $FeCl_3$-induced thrombosis model was utilized.

$FeCl_3$ at an optimum concentration of 42.30 % w/v causes clot/thrombus formation in vein/artery and the weight of the thrombus formed was measured carefully after isolation. The weight of the thrombus formed was used as one of the parameters to find the preventive role of the synthesized compounds on thrombosis. It was observed that almost all the compounds inhibited thrombus formation to variable extents. Compounds (**101** and **110**) were quite active but compound (**105**) again was found to be the most potent in this test. Percent inhibition of thrombosis was also calculated using the thrombus weight. The estimated potency of **105** observed in this model was further confirmed by evaluating it using AV shunt model. Eventually, TTO was measured for all the test compounds. Almost one-third of the compounds significantly inhibited the occlusion for more than 20 min. Compounds (**99**, **102, 104**, **105**, **106**, **107** and **110**) showed better profile in this parameter. The previously hypothesized vasodilatory action of the tested compounds might be responsible for this phenomenon. Compound (**105**) showed TTO of more than 30 min which was equal to the standard drug clopidogrel. Compound (**95**) was found to be the least active amongst all the compounds and was comparable to the unsubstituted diaryl compound (**103**). As several COX inhibiting drugs show moderate to severe gastric ulcerations, the most potent compound (**105**) was evaluated for its propensity to cause gastric ulceration. It was found that it did not show any undesirable side effect at its normal dose of 10 mg/kg, but at higher dose (100 mg/kg), it showed mild ulceration. It was noteworthy that at the same dose of 100 mg/ kg, aspirin, a well-known antithrombotic drug caused severe gastric ulceration. The newly synthesized compound (**105**) increases bleeding time to its optimum level with good *in vitro*, *ex vivo* and *in vivo* profile. These parameters are indicative of fairly good therapeutic profile of compound (**105**) and project the compound (**105**) worthy of further investigation as a new potential drug candidate for thromboembolic diseases.



(**105**)

A novel series of 5,6-diaryl-1,2,4-trizines has been synthesized with several electron withdrawing as well as donating functions attached to the vicinal diaryl rings. *In vitro*, *ex vivo*

and *in vivo* evaluations indicated that some of the compounds showed moderate to potent antiplatelet/antithrombotic activities which could be helpful for the development of new antiplatelet drugs. The most promising compound (**105**) of the series seems to possess a potentially better therapeutic profile.

4.2.3. Biological evaluation of benzoxazinones and anthranilamides (127b-141b, 143a-157a, 143b-157b, 159-173)

4.2.3.1. Human *in vitro* platelet aggregation assay

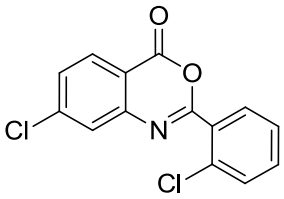
The newly synthesized benzoxazinones and anthranilamides were studied for their *in vitro* platelet aggregation inhibitory activity. The whole human blood aggregation study was done as per the above described procedure. Each reading was taken in triplicate for the test samples, using control and a standard drug aspirin for comparative reading each time. The percent inhibition of platelet aggregation was determined for each test sample in comparison to the control and the standard aspirin. The inhibitory values were calculated accordingly as shown in **Table 3**.

Table 3: *In vitro* platelet aggregation inhibition of benzoxazinones and anthranilamides **(127b-141b, 143a-157a, 143b-157b** and **159-173)**

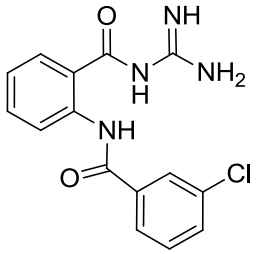
Comp	*In vitro* % Inhibition	Comp	*In vitro* % Inhibition	Comp	*In vitro* % Inhibition	Comp	*In vitro* % Inhibition
127b	52.11	**143a**	40.80	**143b**	10.26	**159**	50.80
128b	43.24	**144a**	40.12	**144b**	45.96	**160**	41.12
129b	35.13	**145a**	43.22	**145b**	38.14	**161**	53.22
130b	10.81	**146a**	54.67	**146b**	53.80	**162**	59.67
131b	54.05	**147a**	36.77	**147b**	36.12	**163**	46.77
132b	20.42	**148a**	42.58	**148b**	48.22	**164**	47.58
133b	11.26	**149a**	**60.54**	**149b**	51.67	**165**	**68.54**
134b	50.00	**150a**	51.00	**150b**	52.77	**166**	50.00
135b	**63.38**	**151a**	53.87	**151b**	49.58	**167**	58.87
136b	52.11	**152a**	10.06	**152b**	**60.54**	**168**	08.06
137b	22.53	**153a**	41.74	**153b**	42.50	**169**	42.74
138b	26.05	**154a**	25.45	**154b**	51.87	**170**	31.45
139b	11.26	**155a**	22.06	**155b**	28.26	**171**	11.26
140b	52.96	**156a**	36.74	**156b**	48.96	**172**	52.96
141b	40.14	**157a**	34.55	**157b**	38.14	**173**	40.14

From the comparative study of the test compounds from benzoxazinone series **(127b-141b)** at the same concentration to aspirin, eight compounds were found to be active as shown in **Table 3**. From the fifteen compounds screened for activity, compound (**135b)** with 2-chloro group substituted on phenyl ring in the benzoxazinone series was found to be the most potent compound, being two times more potent than aspirin. Compounds (**127b, 128b, 131b, 134b, 136b, 140b** and **141b)** were found to be more potent than aspirin.

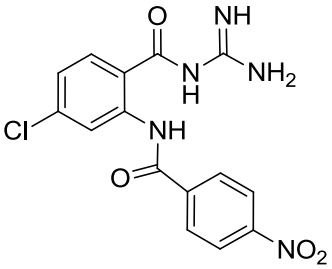
The anthranilamides containing amidino group without substitution on the parent phenyl ring showed good antiplatelet activity. Compounds (**143a-146a, 148a-151a** and **153a**) showed higher inhibition of platelet aggregation than the standard drug aspirin. Compound (**149a)** bearing 3-cloro substituent on phenyl ring was found to be the most active in the series having almost 2-fold inhibition than aspirin. In the same manner, compounds containing 4-chloro substituent on the parent phenyl ring also showed good antiplatelet profile. Compounds (**144b, 146b, 148b-154b** and **156**) exhibited higher activity than aspirin. Among the series, compound (**152b)** with 4-nitrophenyl group was found to be the most potent with 60 % inhibition of platelet aggregation.



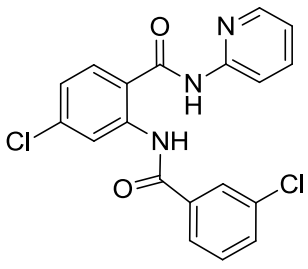
(**135b**)



(**149a**)



(**152b**)



(**165**)

Compounds **(159-173)** having pyridine groups showed good antiplatelet activity as shown in **Table 3**. From the fifteen compounds screened for activity, compound (**165)** with 3-chlorophenyl substituent was found to be the most potent compound being two times more

potent than aspirin. All the compounds of this series were found to be more potent than aspirin except for compounds (**168, 170** and **171)**.

4.3. References

1. Lundstedt, T.; Carlson R; Shabanab R., Optimum conditions for the WiIIgerodt-Kindler reaction. 3. amine variation. *Acta chemica scandinavica* **1987**, 41, 157-63.
2. Furniss, B. S.; Hannaford, A. J., Smith, P. W. G.; Tatchell, A. R., Vogel's text-book of practical organic chemistry, 5th Edition, Eds., Addision-Wesley Longmann Ltd., England **1988**, 673-675, 857-858.
3. Friedel, C.; Crafts, J. M., Sur une nouvelle méthode générale de synthèse d'hydrocarbures, d'acétones. *Comptes rendus* **1877**, 84, 1392.
4. Corey, E. J.; Schaefer, J. P., Studies on the mechanism of oxidation of ketones by selenium dioxide. *Journal of American chemical society*, **1960**, 82, 918-919.
5. Shirude, S. T.; Patel, P.; Giridhar, R.; Yadav, M. R., An efficient and time saving microwave-assisted selenium dioxide oxidation of 1,2-diarylethanones. *Indian journal of chemistry* **2006**, 45 (B), 1080-1085.
6. (a) Weiss, M., Acetic acid-ammonium acetate reactions. 2-isoimidazoles as intermediates in imidazole formation**.** *Journal of the American chemical society* **1952**, 74 (20), 5193-5195. (b) Siddiqui, S. A.; Narkhede, U. C.; Palimkar, S. S.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V., Room temperature ionic liquid promoted improved and rapid synthesis of 2,4,5-triaryl imidazoles from aryl aldehydes and 1,2-diketones or α-hydroxyketone. *Tetrahedron* **2005**, 61, 3539-3546.
7. (a) Rauf, A.; Sharma, S.; Gangal, S., Microwave-assisted efficient one-pot synthesis of 3,5,6-trisubstituted-1,2,4-triazines from fatty acid hydrazides under solvent-free conditions and their antimicrobial activity. *Arkivoc* **2007**, 16, 137–147; (b) Zhao, Z.; Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Lindsley, C. W., Broadening the scope of 1,2,4-triazine synthesis by the application of microwave technology. *Tetrahedron letters* **2003**, 44, 1123–1127; (c) Saad, H. A.; Youssef, M. M.; Mosselhi, M. A., Microwave-assisted synthesis of some new fused 1,2,4-triazines bearing thiophene moieties with expected pharmacological activity. *Molecules* **2011**, 16, 4937–4957; (d) Sangshetti, J. N.; Shinde, D. B., One-pot synthesis and SAR of some novel 3-substituted 5,6-diphenyl-1,2,4-triazines as antifungal agents. *Biorganic and medicinal chemistry letters* **2010**, 20, 742–745; (e) Lee, J. K.; Kim, H. G.; Kim, K. A.; Neunhoffer, H., 1,2,4-Triazine (VII): Synthesis of 6,5'-bis-1,2,4-triazinyls and 6,6'-bis-1,2,4-triazinyls. *Bulletin korean*

chemical society **1998**, 19, 391–394; (f) Saraswathi, T. V.; Srinivasan, V. R., A novel synthesis of 1,2,4-triazines. *Tetrahedron letters* **1971**, 25, 2315–2316; (f) Potewar, T. M.; Lahoti, R. J.; Daniel, T.; Srinivasan, K. V., Efficient synthesis of 3,5,6- trisubstituted-1,2,4-triazines in the Brønsted acidic ionic liquid, 1-*N*-butylimidazolium tetrafluoroborate ([HBIM]BF_4). *Synthetic communication* **2007**, 37, 261–269.

8. Verma, A.; Giridhar, R.; Modh, P.; Yadav, M. R., A facile IL–DMSO assisted synthesis of 5-, 6-, and 7-membered benzo-annelated cyclic guanidines. *Tetrahedron letters* **2012**, 53(24), 2954-2958.
9. (a) Ansari, N.; Khodagholi, F.; Ramin, M.; Amini, M.; Irannejad, H.; Dargahi, L.; Amirabad, A. D., Inhibition of LPS-induced apoptosis in differentiated-PC12 cells by new triazine derivatives through NF-kB-mediated suppression of COX-2. *Neurochemistry international* **2010**, 57, 958–968; (b) Irannejad, H.; Amini, M.; Khodagholi, F.; Ansari, N.; Tusi, S. K.; Sharifzadeh, M.; Shafiee, A., Synthesis and *in vitro* evaluation of novel 1,2,4-triazine derivatives as neuroprotective agents., *Bioorganic and medicinal chemistry* **2010**, 18, 4224–4230.
10. Limanto, J.; Desmond, R. A.; Gauthier, D. R..; Devine, P. N.; Reamer, R. A.; Volante, R. P., A regioselective approach to 5-substituted-3-amino-1,2,4-triazines., *Organic letters* **2003**, 5, 2271–2274.
11. Giridhar, R.; Tamboli, R. S.; Ramajayam, R.; Prajapati, D. G.; Yadav, M. R., Assessment of antiplatelet activity of 2-aminopyrimidines. *European journal of medicinal chemistry* **2012**, 50, 428-432.
12. Broersma, R. J.; Kutcher, L. W.; Heminger, E. F., The effect of thrombin inhibition in a rat arterial thrombosis model. *Thrombosis research* **1991**, 64, 405-412.
13. Hara, T.; Yokoyama, A.; Tanabe, K., DX-9065a, an orally active, specific inhibitor of factor Xa, inhibits thrombosis without affecting bleeding time in rats. *Thrombosis haemostasis* **1995**, 74, 635-639.
14. Dottl, K.; Ripke, O., Blutgerinnung und blutungszeit. in: Medizin und chemie, leverkusen, germany, bayer **1936**, 267-273.
15. Tanaka, A.; Sakai, H.; Motoyama, Y., Antiplatelet agents based on cyclooxygenase inhibition without ulcerogenesis: Evaluation and synthesis of 4,5-bis(4-methoxyphenyl)-2-substituted-thiazoles. *Journal of medicinal chemistry* **1994**, 37, 1189-1199.