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Step-wise, tandem and one-pot syntheses of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-N-arylbenzamidesin water - A green protocol

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ABSTRACT

Background: Eco-friendly, one-pot three-component syntheses of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-N-aryllbenzamides have been developed by combining Di-methyl phthalate with anilines & anthranilamide in water without any catalyst. The reactions involve easy workup, provide excellent yields and use water as solvent making them a green protocol.

Results: As illustrated in **Scheme 1**, a mixture of Di-methyl phthalate **1,** aniline **2a** and anthranilamide **3** was refluxed in water for 90 min resulting in the formation of 2 -(4-oxo-3,4-dihydroquinazolin-2-yl)-N-phenylbenzamide **4a** i.e **4,** R= H (**Scheme 1)**. The structure of the product was assigned on the basis of its spectral properties.

Conclusion: A green synthetic method have been developed for the synthesis of **4a-4i** in water through one-pot, three-component synthesis. Significant rate acceleration of the reaction in water observed and compared to the commonly used green solvents.

Keywords: water, Di-methyl phthalate, anilines, anthranilamide, 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-N-phenylbenzamide.

Background

The development of efficient & environmentally friendly syntheses is a very serious concern in modern organic syntheses[1]. In many synthetic organic processes, solvents pose a very important pollution problem. Thus, the replacement of hazardous solvents with relatively green solvents or the altogether non-use of hazardous solvents in chemical processes is itself a great achievement of green chemistry[2]. Use of water[3,4] as a solvent is the

most desirable achievement of green chemistry because water is a cheap, readily available, non-inflammable, non-toxic and reusable solvent. Furthermore, many organic reactions such as the Diels-Alder reaction, Barbier- Griganard reactions etc proceed very well in water and that too with great selectivity[5-7].

C–N bond formation is an important reaction in organic synthesis because of the importance of nitrogen-containing compounds in the production of pharmaceuticals and fine chemicals [8]. Amides are one of the important functional groups prevalent in organic bio-molecules. A in-depth analysis of the comprehensive medicinal chemistry database revealed that the carboxamide group appears in more than 25% of known drugs. This can be expected, since carboxamides are neutral, stable and have both hydrogen-bond accepting and donating properties[9].

The quinazolinone ring system forms an important class of N-heterocyclic compounds as it is present in a large number of compounds with useful biological properties such as anti-cancer[10], anti-inflammatory[11], anti-convulsant[12], hypotensive[13], and anti-malarial types[14]. On the other hand, Phthalimide derivatives have been widely reported to possess beneficial pharmaceutical effects, like analgesic[15], anti-inflammatory[16] and antiviral[17] etc

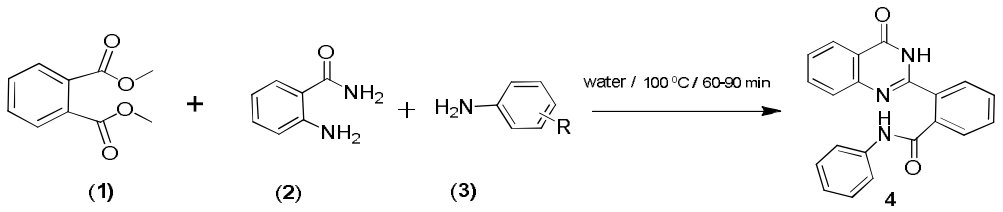
Keeping the above results in mind and in continuation of our earlier work[18], we now wish to report our synthetic studies on reactions of Di-methyl phthalate **l** with anilines **2** and anthranilamide **3** leading to the formation of N-arylbenzamide derivatives which may be potentially biologically active molecules.

RESULTS AND DISCUSSION

As illustrated in **Scheme 1**, a mixture of Di-methyl phthalate **1,** aniline **2a** and anthranilamide **3** was refluxed in water for 90 min resulting in the formation of 2 -(4-oxo-3,4-dihydroquinazolin-2-yl)-N-phenylbenzamide **4a** i.e **4,** R= H (**Scheme 1)**. The structure of the product was assigned on the basis of its spectral properties. Thus, its IR (KBr) showed peaks at 3052 – 3450 cm^{-1} (broad, medium due to the -NH- group) and a 1680 cm^{-1} (sharp, strong, due to the -CO- of amide group). Its ^1H NMR spectrum showed signals at δ 7.05-7.91 (m, 13H, Ar-H), 10.43 (s, 1H, -NH, D_2O exchangeable), 11.51 (s, 1H, -NH, D_2O exchangeable). Its LC-MS showed m/z at 342 due to ($M^{+\cdot}$+1) corresponding to a molecular mass of 341.

Then, this one-pot reaction of **1**(1mmol)**, 2a** (1mmol) and **3** (1mmol) was optimized by doing a series of experiments in the presence of different solvents at different temperatures **(Table 1)**. However, it is greatly notable that the one-pot reaction in water at

100 ^{o}C for 90 min gave reasonably high yield (85%) of the product **4a** compared to other solvents such as glycerol, PEG-600, ethylene glycol, DMF& DMSO (**Table 1, entry 1).**



Scheme 1: Synthesis of 4a-4l by one-pot synthesis.

Table 1 Effect of Solvent & Temperature on one-pot reaction of 1, 2 and 3 yielding 4a.

Entry	Solvent	Temp. /^{o} c	Time (min)	Yield of 4a (% molar)
1	**H_2O**	RT	300	Nil
2	**H_2O**	**100**	**90**	**85**
3	Glycerol	RT	300	Nil
4	Glycerol	100	120	85
5	PEG-600	RT	300	Nil
6	PEG-600	100	150	70
7	Ethyleneglycol	RT	300	Nil
8	Ethyleneglycol	100	150	60
9	DMF	RT	300	30
10	DMF	100	150	55
11	DMSO	RT	300	40

In order to further expand the scope of this protocol, one pot reaction of of Di-methyl phthalate **1**, with substituted anilines **2a-i** & anthranilamide **3** was investigated and a new series of N-arylbenzamides were obtained in good yields **(Table-2)**

Table-2 Synthesis of 4a-4i involving condensation of 1 with 2a-2i & 3.

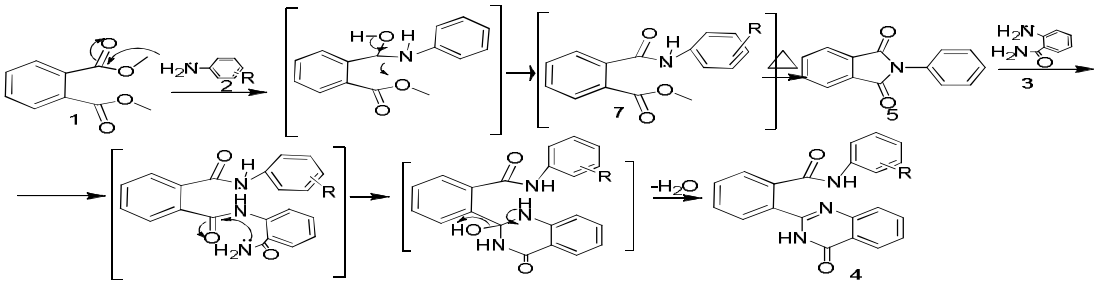
Entry	Product	R	Time (min) *	**Yield of 4a (% molar)**	M.P(^{o}C)
1	**4a**	H	90	75	220
2	**4b**	4-NO_2	100	80	214
3	**4c**	4-CH_3	120	70	200
4	**4d**	4-Cl	90	85	190
5	**4e**	4-OH	120	75	221
6	**4f**	2-Cl	100	70	195
7	**4g**	4-OCH_3	120	72	205
8	**4h**	4-F	90	80	220
9	**4i**	4-Br	120	82	190

***** Based on TLC indication for completion of reaction

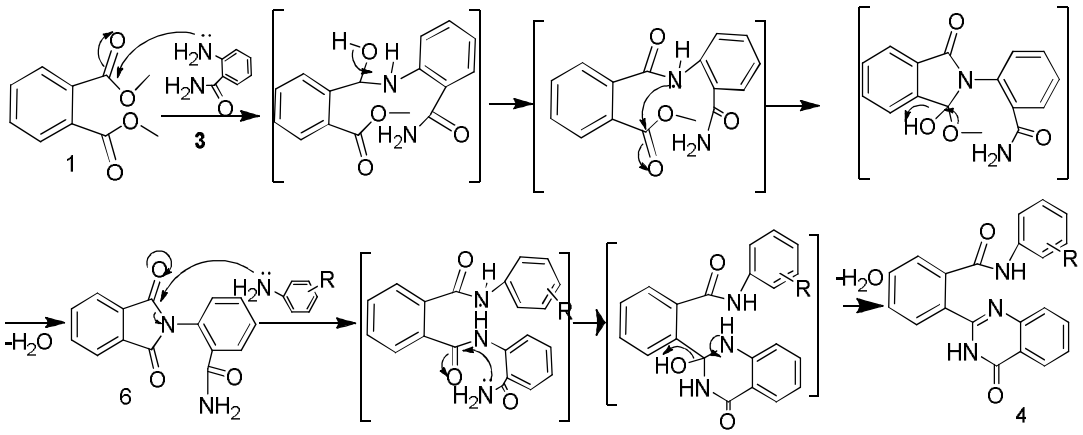
Two probable mechanisms, namely **mechanism-I (Scheme-2), mechanism-II (Scheme-3).** have been proposed to account for the formation of **4** in the one-pot synthesis from **1, 2 & 3.** In the **mechanism-I,** Di-methyl phthalate **1** reacts with aniline **2** to form the imide intermediate **5** which is then attacked by anthranilamide **3** to form **4** in about two steps. Evidence for the above mechanism comes from the fact that the intermediate **5a** could be prepared separately by reaction between **1** and **2a** and then treated with **3** in water to obtain **4a**. **(see Scheme-4)**.

Plausible mechanisms for the formation of 4 from 1, 2 & 3 by one pot synthesis.

Mechanism I: Scheme-2

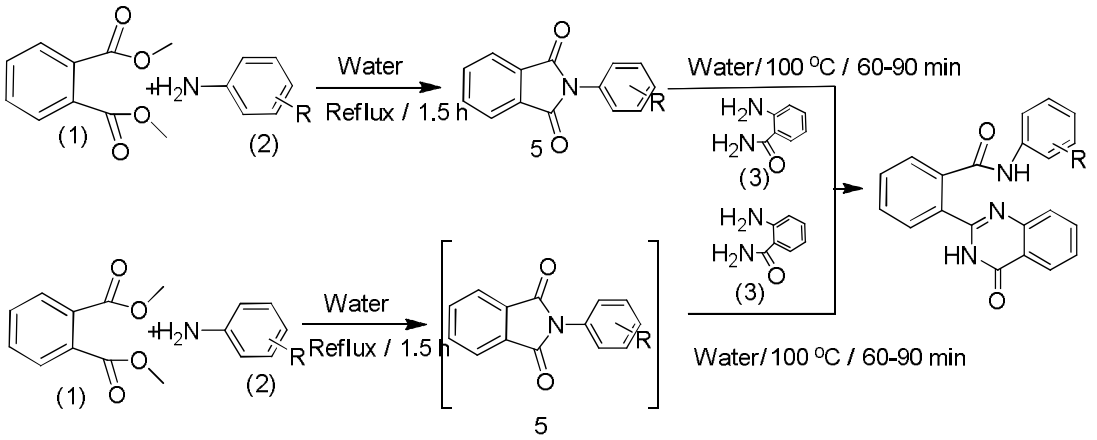


Mechanism-II: Scheme-3

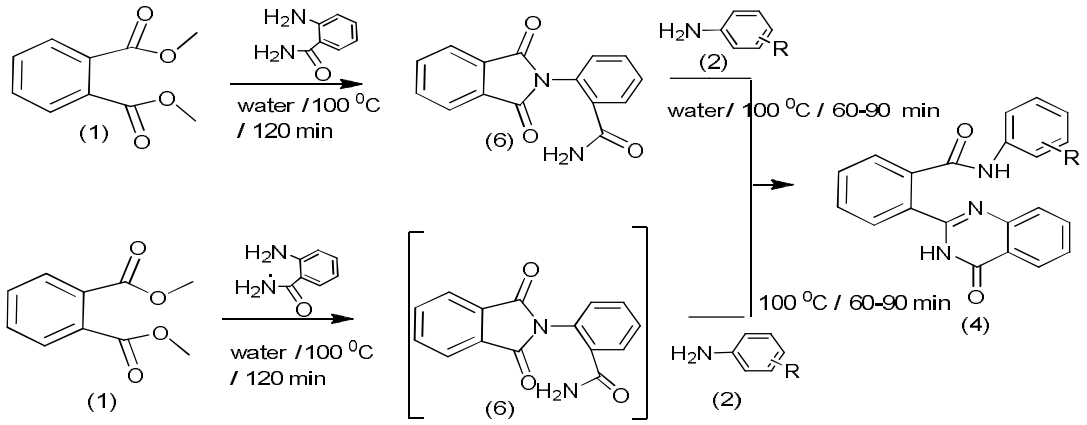


In the **mechanism-II,** shown in **Scheme-3**, reaction of Di-methyl phthalate **1** with anthranilamide **3** yields the intermediate **6** which is then attacked by **2** to form **4** in two steps. Evidence for this mechanism comes from the fact that, the intermediate **6** was prepared separately by the reaction between **1** and **3**, which was then treated with **2** in water to obtain **4 (See Scheme-5)**.

It thus appears that both the **mechanisms I** and **II** are operating in this reaction. The difference between these two mechanisms is that in **mechanism-I** involves a prior condensation of **1** with **2** followed by condensation with **3** whereas **mechanism-II** involves initial condensation of **1** with **3** followed by condensation with **2**.



Scheme 4: Synthesis of 4 by step-wise &Tandem reaction in water



Scheme 5: Alternative Synthesis of 4 under step-wise & Tandem conditions in water.

Encouraged by above results, synthesis of **4a-4i** have also been achieved successfully using tandem synthesis involving step-wise sequences (see Scheme 3 & 4).

The best method among one pot, step-wise and tandem conditions concluded from following observations.

Table-3 Comparative study between one-pot, tandem and step-wise methode

METHOD	TIME	YIELD of 4a (Molar)
ONE POT	90 Min	85%
TANDEM	110 Min	75%
STEPWISE-1 1+2 → 5 (3) →	1+2 → 5 40 Min 5 (3) → 4 70 Min Total : 40+70 =110 M	1+2 → 5 80% 5 (3) → 4 60% 80 X 0.60 =
STEP-WISE –2 1+3 → 6 (2) →	1+3 → 6 50 Min 6 (2) → 4 70 Min Total : 50+70 =120	1+3 → 6 80% 6 (2) → 4 60% 80 X 0.60 =

It is evident that from Table-3 that the one – pot method is the best among the three.

EXPERIMENTAL SECTION

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel – G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO – d_6 using TMS as internal standard using 400 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument. Starting materials **1, 2 & 3** were obtained from commercial sources and used as such.

General procedure for preparation of 4 from 1, 2 & 3 by one-pot synthesis

A mixture of **1** (10 mM), **2** (10 mM), **3** (10 mM), and water (20 ml) was refluxed at 100 ^{o}C for 90-120 min. At the end of this period, a colourless solid separated out from the reaction mixture which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. Further the filtrate was subjected to ethyl acetate extraction, but there was no substantial amount of product **4** in the filtrate.

4a (i.e 4, R=H); Yield=0.27gm (75%); M.P: 220°C (EtOH):For Spectral data See

RESULTS AND DISCUSSION

4b (i.e 4, R=NO_2); Yield= 0.32 gm (80%); M.P: 214°C (EtOH) ; IR (KBr): 3710-3510 cm^{-1} (amide –NH), 1773 cm^{-1} (sharp, strong, -CO- of amide group). ^{1}H NMR at δ 9.4 (s, 1H, -NH, D_2O exch); δ 10.5 (s, 1H, -NH, D_2O exch); δ 6.8-7.9 (m, 12 H, Ar-hydrogens); LC-MS; m/z = 387 ($M^{+\cdot}$+1).

4c (i.e 4, R=CH_3); Yield= 0.27 gm (70%); M.P: 200°C (MeOH) ; IR (KBr): 3690 -3510 cm^{-1} (amide –NH), 1763 cm^{-1} (sharp, strong, -CO- of amide group). ^{1}H NMR δ 2.1 (-CH_3 -3H); δ 9.6
(s, 1H, -NH, D_2O exch); δ 10.4 (s, 1H, -NH, D_2O exch); δ 6.8-7.9 (m, 12 H, Ar-hydrogens); LC-MS; m/z = 356 ($M^{+\cdot}$+1).

4d (i.e 4, R=Cl); Yield= 0.30 gm (85%); M.P: 190°C (MeOH) ; IR (KBr): 3690-3520 cm^{-1} (amide –NH), 1789 cm^{-1} (sharp, strong, -CO- of amide group). ^{1}H NMR δ 9.1 (s, 1H, -NH, D_2O exch); δ 10.8 (s, 1H, -NH, D_2O exch); δ 6.8-7.9 (m, 12 H, Ar-hydrogens); LC-MS; m/z = 376
($M^{+\cdot}$+1).

4e (i.e 4, R=OH); Yield=0.27gm (75%); M.P: 221°C (EtOH+Water) ; IR (KBr): 3700-3520 cm^{-1} (amide –NH), 1753 cm^{-1} (sharp, strong, -CO- of amide group). ^{1}H NMR at δ 4.1 (s, 1H, -OH, D_2O exch); δ 9.1 (s, 1H, -NH, D_2O exch); δ 9.9 (s, 1H, -NH, D_2O exch); δ 6.4-7.9 (m, 12 H, Ar-hydrogens); LC-MS; m/z = 376 ($M^{+\cdot}$+1).

4f (i.e 4, R=2-Cl); Yield=0.28gm (70%); M.P: 195°C (MeOH) ; IR (KBr): 3710-3550 cm^{-1} (amide –NH), 1773 cm^{-1} (sharp, strong, -CO- of amide group). ^{1}H NMR, δ 9.2 (s, 1H, -NH, D_2O exch); δ 10.8 (s, 1H, -NH, D_2O exch); δ 6.8-7.9 (m, 12 H, Ar-hydrogens); LC-MS; m/z = 376 ($M^{+\cdot}$+1).

4g (i.e 4, R=OCH_3); Yield=0.29 gm (72%); M.P: 205°C (EtOH+MeOH) ; IR (KBr): 3700-3500 cm^{-1} (amide –NH), 1783 cm^{-1} (sharp, strong, -CO- of amide group). ^{1}H NMR, δ 4.1 (-O-CH_3-3H); δ 9.8 (s, 1H, -NH, D_2O exch) δ 10.1 (s, 1H, -NH, D_2O exch); δ 6.8-7.9 (m, 12 H, Ar-hydrogens); LC-MS; m/z = 372 ($M^{+\cdot}$+1).

4h (i.e 4, R=F); Yield=0.31 (80%); M.P: 220°C (EtOH) ; IR (KBr): 3720-3610 cm^{-1} (amide –NH), 1783 cm^{-1} (sharp, strong, -CO- of amide group). Its ^{1}H NMR δ 9.8 (s, 1H, -NH, D_2O exch); δ 10.1 (s, 1H, -NH, D_2O exch); δ 6.8-7.9 (m, 12 H, Ar-hydrogens); LC-MS; m/z = 359 ($M^{+\cdot}$+1).

4i (i.e 4, R=Br); Yield= 0.36gm (82%); M.P: 190°C (EtOH+Water) ; IR (KBr): 3690-3520cm^{-1} (amide –NH), 1783 cm^{-1} (sharp, strong, -CO- of amide group). ^{1}H NMR δ 9.8 (s, 1H, -NH, D_2O exch); 10.1 (s, 1H, -NH, D_2O exch); δ 6.8-7.9 (m, 12 H, Ar-hydrogens); LC-MS; m/z = 420 ($M^{+\cdot}$+1).

Preparation of 5a

A mixture of **1** (10 mM), **2a** (10 mM) and water (20 ml) was refluxed for 90 min At the end of this period, a colourless solid separated out from the reaction mixture which was collected by filtration. The solid was washed with water (10 ml) and dried. The product was recrystallized from a

Procedure for preparation of 4afrom 5a & 3

A mixture of **5a** (10 mM), **3** (10 mM) and water (20 ml) was refluxed at 100 °C for 60-90 min. At the end of this period, a colourless solid separated out from the reaction mixture which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. The crude product was recrystallized from a ethanol solvent to obtain **4a**

Preparation of 4a from 1, 2a &3 by tandem reaction

A mixture of **1** (10 mM), **2a** (10 mM) and water (20 ml) was stirred at RT for 15-20 min when a colourless solid separated out from the reaction mixture. Then, to this solution,**3** (10 mM) was added and the mixture refluxed at 100°C for 90-95 min. Another colourless solid separated out from reaction mixture which was collected by filtration.

Preparation of 6 from 1 & 3

A mixture of **1** (10 mM), **3** (10 mM) and water (20 ml) was refluxed at 100 °C for 90 min.. At the end of this period, a colourless solid separated out from the reaction mixture which was collected by filtration. The latter solid was washed with water (10 ml) and dried. The crude product was recrystallized from methanol to obtain **6**.

Preparation of 4a from 6 & 2a

A mixture of **6** (10 mM), **2a** (10 mM) and water (20 ml) was refluxed at 100 °C for 60-90 min. At the end of this period, a colourless solid separated out from reaction mixture which was collected by filtration. The isolated solid was washed with hexane (10 ml) and dried. The product was recrystallized from a methanol solvent to obtain **4a**.

Procedure for preparation of 4a by second tandem methode

A mixture of **1** (10 mM), **3** (10 mM) and water (20 ml) was refluxed at 100 ^{o}C for 110-120 min. A colourless solid separated out from reaction mixture. Then, to this mixture at RT, **2a** (10 mM) was added and refluxed at 100 ^{o}C for 60-90 min. A colourless solid separated out from reaction mixture which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. The product was recrystallized from suitable methanol to obtain **4a**.

CONCLUSION

In summary, practical and green synthetic methods have been developed for the synthesis of **4a-4i** in water through one-pot, three-component synthesis. Significant rate acceleration of the reaction in water observed and compared to the commonly used green solvents. Through this reaction, variety of **4a-4i** was synthesized in water in good yield**.**

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contribution: BSN carried out the experimental work. VRR performed the statistical analysis and drafted the manuscript. All authors have gone through the final manuscript and approved it.

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REFERENCES

1. (a)Istvan TH, Paul T A. Introduction: Green Chemistry. Chem. Rev. 2007, 107, 2167. (b) T. Horvath, I. Green Chemistry. Chem. Rev. 2002, 35, 685-720.
2. Lindström, UK. Stereoselective Organic Reactions in Water. Chem. Rev. 2002, 102, 2751. (b) Li CJ. Organic Reactions in Aqueous Media with a Focus on Carbon−Carbon Bond Formations: A Decade Update. Chem. Rev. 2005, 105, 3095-3125.
3. (a) Li CJ. Organic reactions in aqueous media - with a focus on carbon-carbon bond formation, Chem. Rev. 1993, 93, 2023. (b) Li CJ, Chen L. Organic chemistry in water Chem. Soc. Rev. 2006, 35, 68. (c) Dallinger D, Kappe CO. Microwave-Assisted Synthesis in Water as Solvent Chem. Rev. 2007, 107, 2563. (d) Chanda A, Fokin VV. Organic Synthesis "On Water" Chem. Rev. 2009, 109, 725. (e) Klijn JB, Engberts, FN. Organic chemistry: Fast reactions `on water. Nature, 2005, 435, 746-765.
4. (a) Li CJ,. Chan TH. Organic Reactions in Aqueous Media. Wiley, New York, 1997; (b) Narayan S, Muldoon J, Finn MG, Fokin VV, Kolb HC, Sharpless KB. "On water": unique reactivity of organic compounds in aqueous suspension Angew. Chem. Int. Ed. 2005, 44, 3275-3296.
5. (a) Rideout DC, Breslow R. Hydrophobic acceleration of Diels-Alder reactions J. Am. Chem. Soc. 1980, 102, 7816. (b) Matloubi Moghaddam F, Hojabri L, Taheri S, Pirani P. Synthesis of Functionalized 5H-Spiro[furan-2,2'-indene]-1',3',5-triones from Primary Amines, Acetylenic Esters and Ninhydrin. J. Iran. Chem. Soc., 2010, 7(3), 781-798.
6. (a) Liu XY, Che CM. The Cross-Dehydrogenative Coupling of C-H bonds. A Versatile Strategy for C-C Bond Formations. Angew. Chem. Int. Ed. 2008,47, 3850. (b) Herrer Tas CI, Yao X, Li Z, Li CJ. Reactions of C-H bonds in water. Chem. Rev., 2007, 107, 2546-2568.
7. Zhou F, Li CJ. The Barbier–Grignard-type arylation of aldehydes using unactivated aryl iodides in water. Nat. Commun. 2014, 5, 4254-4278.

8. Tamaoki T, Nomoto H, Takahishi I, Kato Y, Morimoto M, Tomita F. Staurosporine, a potent inhibitor of phospholipid/Ca++dependent protein kinase .Biochem. Biophys. Res. Commun. 1986, 135, 397–410.
9. (a)Montalbetti, Cristian AGN, Falque V. Amide bond formation and peptide couplingTetrahedron 2005, 61, 10827; (b) Ghose AK, Viswanadhan VN, Wendoloski JA. Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases J. J. Comb. Chem. 1999, 1, 55-68.
10. Sirisoma N, Pervin A, Zhang H, Jiang S, Willardsen J, Anderson B, Mather G, Pleiman M, Kasibhatla S, Tseng B, Drewe J, Xiong Cai S. Discovery of N-(4-Methoxyphenyl)-N,2-dimethylquinazolin-4-amine, a Potent Apoptosis Inducer and Efficacious Anticancer Agent with High Blood Brain Barrier Penetration. J Med Chem. 2009, 52, 2341-2378.
11. Burbuliene MM, Jakubkiene V, Mekuskiene G, Udrenaite P, Smicius P. Synthesis and anti-inflammatory activity of derivatives of 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thiones. Farmaco. 2004, 59, 767-774.
12. Alagarasamy M, Meena S, Revathi R, Vijaya kumar S, Ramesh KV. Synthesis of some novel 2-mercapto-3(substituted amino)5,6,7,8-tetrahydro-3H-benzo[4,5] thieno[2,3-d]pyrimidin-4-ones as analgesic and anti inflammator agents. Arkivoc. 2006,58, 149-157.
13. Ozaki K, Yamada Y, Onine T, Ishizuka T, Iwasawa Y. Studies on 4(1H)-Quinazolinones. 5. Synthesis and Anti inflammatory Activity of 4(1H)-Quinazolinone Derivatives. J Med Chem. 1985,28,568-576
14. Nilantha S, Azra P, Hong Z, Songchun, J, Adam W, Mark A, Gary M, Christopher M, Shailaja K, Ben, John D, Sui X. Discovery of N-(4-Methoxyphenyl)-N,2-dimethylquinazolin-4-amine, a Potent Apoptosis Inducer and Efficacious Anticancer Agent with High Blood Brain Barrier Penetration. J Med Chem. 2009, 52, 2341-2351.
15. Antunes R, Batista H, Srivastava RM, Thomas G, Araujo C C. New phthalimide derivatives with potent analgesic activity: II. Bio.org Med. Chem .Lett 1998, 21,3071-3076
16. Lídia L, Paulo C, Alexandre M, Carlos A, Fraga M, Claire L, Vera Lúcia M, Eliezer JB. Synthesis and anti-inflammatory activity of phthalimide derivatives, designed as new thalidomide analogues. Bioorg. Med. Chem. 2002, 9, 3067-3073.
17. Alaa AM, Abdel A. Novel and versatile methodology for synthesis of cyclic imides

and evaluation of their cytotoxic, DNA binding, apoptotic inducing activities and molecular modeling study. Eur. J. Med. Chem. 2007,42, 614-626.

18. (a) Reddy Y D, Reddy ChVR, and Dubey PK. Water mediated, environmentally friendly, step-wise, tandem & one-pot syntheses of 2-(1H-benzo[d]imidazole-2-yl)-N-arylbenzamides RSC Adv. 2014, 4 2974-2979. (b) Kumar P P, Reddy Y D, Reddy Ch V R, Devi B R Dubey PK. 2014 One pot, three-component synthesis of novel 3,4-dihydrophthalazin-2(1H)-yl-4-phenyl-4H-pyrans. Tetrahedron Letters 2014, 55, 2177–2182.