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Synthesis of some New Schiff Bases Containing Acridone Moiety

Attalla M. Sheat
Department of Chemistry/ College of Science/ University of Mosul
E- mail: attalsharifi@yahoo.com

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ABSTRACT

The 2-[(4'-amino-3,3'-dimethylbiphenyl-4-yl)amino]benzoic acid (II) was synthesized by Ullmann-Goldberg coupling by reaction of 3,3'-dimethylbiphenyl-4,4'-diamine (I) with 2-chlorobenzoic acid. The compound (II) was cyclized by poly phosphoric acid (PPA) to give 2-[(4-amino-3-methyl)phenyl]-4-methylacridin-9 (10*H*)-one (III). New Schiff bases (IVa-j) and (Va-d) has been prepared by reaction of compound (III) with aromatic aldehydes and cyclic ketones respectively.

Keywords: Schiff bases, Acridone moiety.

تحضير بعض قواعد شيف الجديدة المحتوية على جزيء الاكريدون

الملخص

استخدم تفاعل اولمن-كودبرج لتحضير 2-[(4′-امينو-3و3′- داي مثيل باي فنيل -4- يل) امينو] حامض البنزويك (II) وذلك من تفاعل 3و3′-دايمثيل باي فنيل-4و4′-دايامين (I) مع 2– كلورو حامض البنزويك، ثم حولقة المركب (II) بواسطة حامض الفسفوريك المتعدد (PPA) إلى 2- [(4– امينو–3 – مثيل) فنيل) – 4– مثيل اكريدين -9 (H10) – اون (III). ثم مفاعلة المركب (III) مع بعض الالديهايدات الاروماتية والكيتونات الحلقية ليعطي قواعد شيف الجديدة (IVa-j) و (Va-d) على التوالي.

الكلمات الدالة: قواعد شيف، زيء الاكريدون.

INTRODUCTION

The basic tricyclic framework can be decorated with suitable substituents to confer specificity against both prokaryotic and eukaryotic targets which have given acridines a respectable reputation in the history of chemotherapy (Velingker and Dandekar, 2009). Fused heterocyclic acridone is one of scaffolds known to be associated with biological activities due to the pharmacological activities of its nucleus. It has a carbonyl group and nitrogen atom at 9 and 10 position respectively.

Acridones of natural and synthetic origins are known to possess a wide variety of biological activities (Ajala and Okoro, 2012), including inhibitory action against viruses (Goodell *et al.,* 2006), and used as anticancer (Amareswarao *et al*., 2016, Kandeel *et al*., 2016), anti-tumor (Huang *et al*., 2015), anti-leukemia (Wang, *et al*., 2013), anticonvulsant (Mohammad *et al*., 2016), antimicrobial (Kadryavtsera *et al*., 2015; Gupta *et al.,* 2015), anti-malarial (Valdes, 2011), anti-proliferative (Ugarte *et al*., 2012), and it also used as acetylcholinesterase inhibitor (Khanposhtani *et al*., 2015).

EXPERIMENTAL

Melting point was determined using Electro thermal IA9000 Digital-series melting point apparatus, (uncorrected). All reagents and chemicals were used from commercial sources. The solvents were dried by standard procedures. The purity of the compounds was ascertained by thin layer chromatography (TLC) on pre-coated silica gel glass plates using either UV radiation or iodine staining for visualization. Column chromatography was carried out using 100–200 mesh

silica gel (BDH). IR spectra were recorded using FT-IR-600 Bio Tech Engineering Management spectrophotometer UK using KBr disc.^{1}H-NMR and ^{13}C-NMR spectra were obtained from a Bruker-avance 300 MHz, NMR spectrometer. The chemical shifts are reported as δ (ppm) for the DMSO- d_6 solution using TMS as internal standard. The coupling constant, J(Hz) in that order with the use of the following abbreviations; s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

Synthesis of 2[(4'-amino-3,3'-dimethylbiphenyl-4-yl)amino]benzoic acid (II) (Mei *et al*., 2006; Wolf and Mei, 2003).

A mixture of 3,3'-dimethylbiphenyl-4,4'-diamine (I) (25 mmol, 5.3 g), 2-chlorobenzoic acid (24 mmol, 3.8 g), anhydrous K_2CO_3 (30 mmol, 4.1 g), Cu powder (0.05 g), and Cu_2O (0.05 g) in 5 ml of 2-ethoxyethanol was refluxed at 130 ^{o}C for 3 hours. The cooled reaction mixture was poured into 30 ml of water. Charcoal was then added and the solution was filtered through celite. The crude product was obtained by a precipitation. Acidification of the filtrate with diluted HCl, and subsequent recrystallization from acetone/water (1:8). The crystals were dissolved in 100 ml of 5% aqueous Na_2CO_3. The solution was filtered through a celite and the product was precipitated by acidification of the filtrate to afford acid (II), (6.18 g, 55 %), as a green powder (m.p = 229 – 231 ^{o}C), (R_f = 0.55) (chloroform: methanol 9.5: 0.5).

Synthesis of 2-(4-amino-3-methylphenyl)-4-methylacridin-9(10*H*)-one (III) (Denny *et al.,* 1977; Jameel and Sheat, 2014)

The acid (II) (5g) was heated with polyphosphoric acid (PPA) (50 ml) at 120 - 130 ^{o}C until a homogeneous solution resulted. The heating was continued for 3hrs. The product was precipitated by addition of H_2O and basification with NH_4OH. The solid material was filtered off by vacuum and washed several times with water then air dried to give (4.1g, 87 %), as green powder (m.p > 325^{o}C dec), (R_f = 0.67) (chloroform: methanol 9.5: 0.5).

Synthesis of 2-[4-(benzylidineamino)-3-methylphenyl]-4-methylacridin-9(10*H*)-one(IVb-j), (Va-d) (Kannappan *et al*., 2009; Belwal and Joshi, 2012) (General procedure)

To a solution of compound III (0.2 g, 0.63 mmol) in dry methanol (25 ml), benzaldehyde (0.06 g, 0.63 mmol) was added. The resulted solution was refluxed with stirring for at least 6 hours. The proceeding of the reaction was monitored by TLC. The mixture was cooled and left overnight. The solid product was filtered off and dried in air (40%, m.p = 275^{o}C). The same procedure was used to prepare the compounds (IVb-j) and (Va-d) by mixing of (0.63 mmol of compound (III) with appropriate substituted benzaldehyde and cyclic ketones. Table (1) summarizes the physical properties and spectral data for compounds (IVa-j) and (Va-d). (R_f = chloroform: methanol 9.5: 0.5).

Table 1: The Physical properties and the FT-IR spectral data (in cm^{-1}) for compounds (IVa-j) and (Va-d)

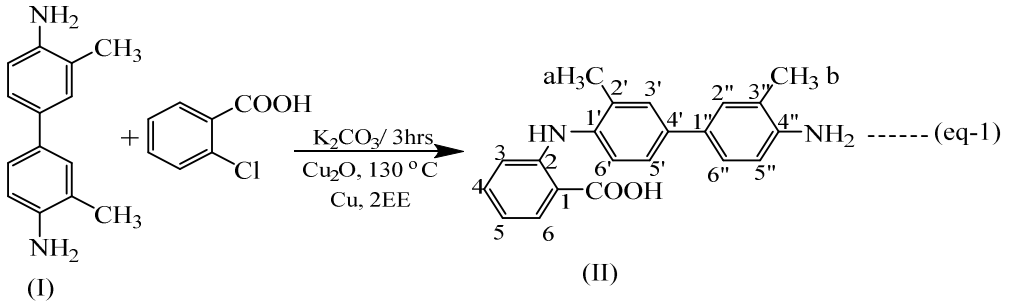
Compd. No.	X	m.p °C	R_f	color	Yield %	N-H Str.	C=O Str.	C=N Str.	C=C Str.
Iva	H	275	0.82	Greenish-yellow	40	3307-3202	1623	1591	1571
IVb	4-Br	305	0.8	Green	55	3335-3260	1622	1590	1568
IVc	3-NO_2	310-312	0.67	Reddish-Brown	57	3355-3248	1625	1595	1568
IVd	4-NO_2	320-322	0.65	Red	60	3336-3215	1630	1602	1565
IVe	2-OH	300-302	0.64	Yellow	35	3365-3210	1633	1605	1567
IVf	4-OH ,3-OCH_3	270-272	0.63	Yellow	32	3332-3277	1625	1595	1561
IVg	4-OCH_3	265-267	0.71	Yellow	35	3368-3313	1627	1603	1571
IVh	4-$N(CH_3)_2$	306-308	0.75	Yellowish -Black	30	3350-3221	1635	1601	1565
IVi	2-COOH	282-284	0.59	Brown	69	3361-3232	1623	1598	1567
IVj	4- Cl	258-260	0.78	Yellow	72	3380-3227	1638	1593	1571
Va		142-144	0.66	Black	35	3370-3225	1625	1591	1572
Vb		120-122	0.69	Brown	40	3375-3226	1625	1601	1595
Vc		90(d)	0.63	Brown	38	3378-3220	1623	1595	1575
Vd		170(d)	0.61	Brown	35	3360-3215	1630	1597	1572

d. decomposition

RESULTS AND DISCUSSION

Synthesis of 2[(4'-amino-3,3'-dimethylbiphenyl-4-yl)amino]benzoic acid (II).

2[(4'-Amino-3,3'-dimethylbiphenyl-4-yl)amino]benzoic acid (II) was prepared by mixing 3,3'-dimethylbiphenyl-4,4'-diamine (I) with 2-chlorobenzoic acid, in presence anhydrous potassium carbonate as a base, 2- ethoxy ethanol as a solvent, cuprous oxide and copper metal as a catalyst as shown in the following equation.

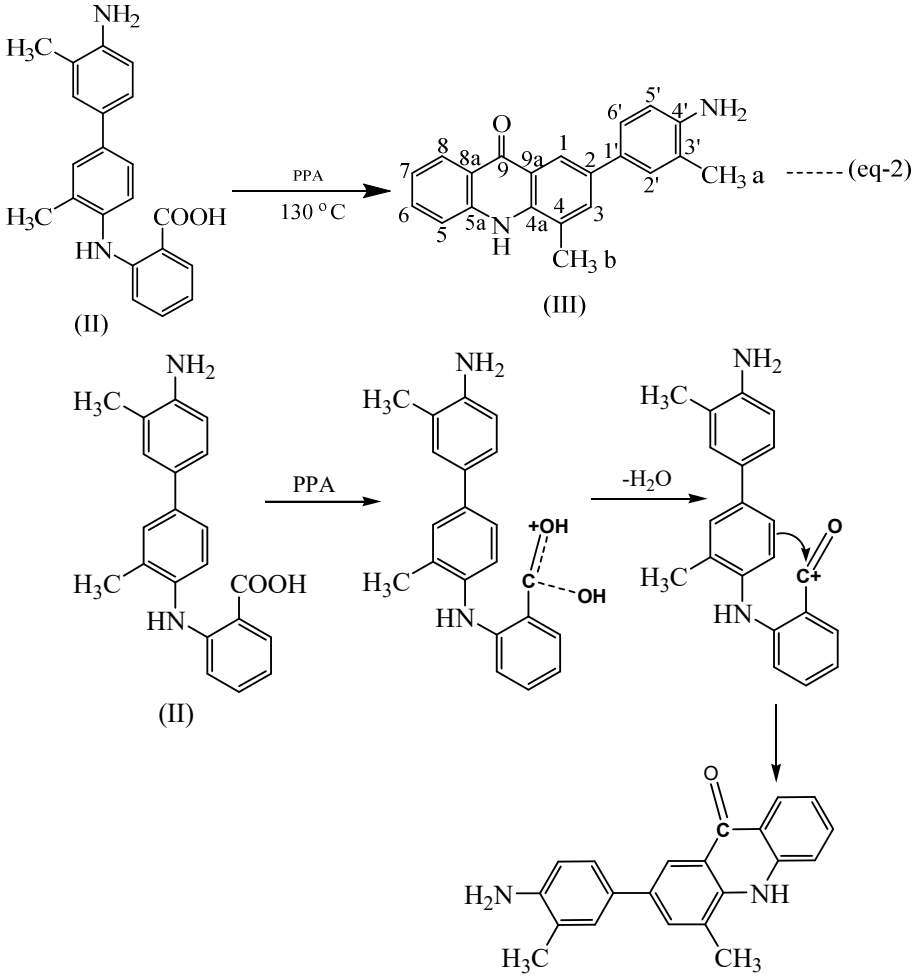


(I) (II)

The structure of the acid(II) was identified by FT-I.R, ^{1}H-NMR, and ^{13}C-NMR spectral data. The IR spectra showed the following main absorption bands (cm^{-1}) at: 1598 (C=C), 1655 (C=O), 3310-2350 (NH, NH_2), 3460 (OH) (Jameel and Mohammed, 2011). ^{1}H-NMR spectrum showed the following chemical shifts (δ, ppm). δ = 2.12 (s, CH_3 b), 2.23 (s, CH_3 a), 3.37 (br, NH_2), 6.66-6.91 (m, 11H, Ar-H, N-H), 9.52 (br, 1H, OH). ^{13}C-NMR δ = 18.09 (CH_3b), 18.30 (CH_3a), 112 (C_1), 113.72 ($C_{5''}$), 114.78 (C_5), 116.94 (C_3), 121.81 ($C_{3''}$), 123.78 ($C_{4'}$), 124.15 ($C_{5'}$), 124.90 ($C_{6''}$), 127.91 (C_6), 128.38 ($C_{1''}$), 128.38 ($C_{4'}$), 132.26 ($C_{3'}$), 132.26 ($C_{2''}$), 134.60 ($C_{2'}$), 136.29 (C_4), 137.29 ($C_{1'}$), 146.53 (C_2), 148.63 ($C_{4''}$), 170.75 (C=O). (Girohar *et al*., 2010).

Synthesis of 2-(4-amino-3-methylphenyl)-4-methylacridin-9(10*H*)-one (III).

The compound (III) was prepared by cyclization of the acid (II) using (PPA) according to the following equation. The mechanism of this reaction (scheme 1) involves cyclodehydration of the corresponding acid (Ganan, 1973).

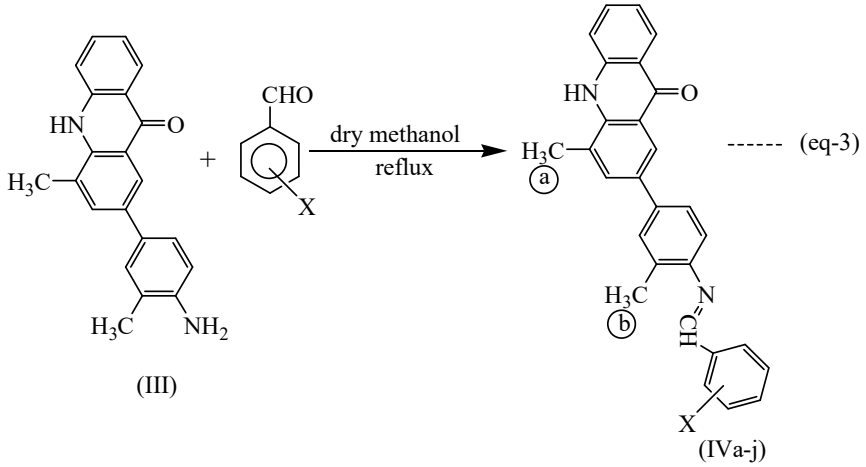


Scheme (1)

The structure of compound (III) was identified by FT- I.R , ^{1}H-NMR, and ^{13}C-NMR spectral data. The IR spectra showed the following main absorption bands (cm^{-1}) at 1590 (C=C), 1623 (C=O), 3340-3250 (NH,NH_2) (Ganan, 1973). ^{1}H-NMR spectrum showed the following chemical shifts (δ, ppm). δ = 2.15 (s, CH_3 a), 2.64 (s, CH_3 b), 3.49 (s, NH_2), 6.71- 8.32 (m, 9H, Ar-H), 10.66 (s, 1H, NH). ^{13}C-NMR δ = 18.09 (CH_3b), 18.44 (CH_3a), 114 ($C_{5'}$), 118.65 (C_5), 119.63 (C_{8a}), 119.63 (C_{9a}), 120.64 (C_4), 121.59 (C_7), 122.00 ($C_{3'}$), 124.99 (C_1), 126.25 ($C_{2'}$), 126.25 ($C_{6'}$), 127.48 (C_8), 128.38 (C_3), 132.60 (C_6), 133.52 (C_2), 134.27 ($C_{1'}$), 141.37 (C_{5a}), 143.27 (C_{4a}), 146.67 ($C_{4'}$), 177.60 (C_9) (Avellaneda *et al*., 2002).

Synthesis of 2-[4-(substituted-benzylidineamino)-3-methylphenyl]-4-methyl acridin-9(10*H*)-one (IVa-j).

The compounds (IVa-j) were prepared by heating an equimolar of compound (III) with aromatic aldehydes in dry methanol according to the following equation.

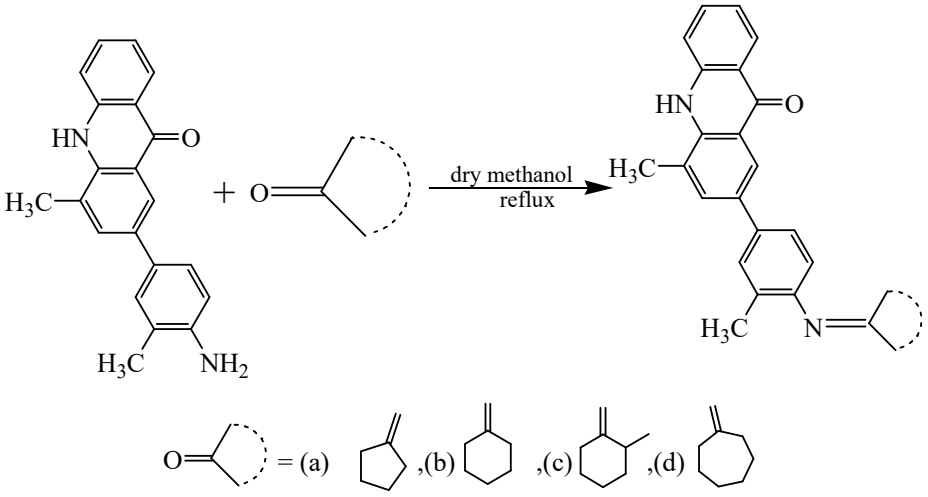


X = (a) H, (b) 4-Br, (c) 3-NO_2, (d) 4-NO_2, (e) 2-OH, (f) 4-OH,3-OMe, (g) 4-OCH_3, (h) 4-$N(CH_3)_2$, (i) 2-COOH, (j) 4-Cl

The structures of these compounds were identified by FT-I.R and ^{1}H-NMR spectral data; IR spectra showed a main absorption bands (cm^{-1}) Table (1) at: 3380 – 3215 (N-H), 1638–1622 (C=O), 1605–1591 (C=N), 1565–1571 (C=C) (Hodgeman and Prager, 1971). ^{1}H-NMR spectrum for compound (IVd) showed the following chemical shifts (δ, ppm). δ = 2.47 (s, CH_3 a), 2.72 (s, CH_3 b), 7.28 -8.41(m, 13H, Ar-H), (s, 1H, HC=N), 10.74 (s, 1H, NH). ^{1}H-NMR spectrum for compound (IVi) showed the following chemical shifts (δ, ppm): δ = 2.75 (s, CH_3b), 2.68 (s, CH_3a), 6.70 (d, 1H, J = 7.2Hz), 6.70 - 8.25 (m, 14H, Ar-H, COOH), 8.33 (s, 1H, HC=N), 10.71 (s, 1H, NH). (Drogon *et al.,* 2010; Gao *et al.,* 2012).

Synthesis of 2-[4-(cycloalkylidineamino)-3-methylphenyl]-4-methylacridin-9(10*H*)-one (Va-d).

These compounds were prepared by heating of equimolar of compound (III) with various cycloketones in dry methanol as shown in the following equation.



The structures of these compounds (Va-d) were identified by the I.R spectral data. The I.R spectra of these compounds showed a main absorption bands (cm^{-1}), Table (1) at 3378-3215 (N-H), 1623-1630 (C=O), 1591-1601 (C=N), 1595-1672 (C=C).

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REFERENCES

Ajala, A.O.; Okoro, C.O.; (2012). QSAR Topomer Co MFA studies on 10 N- substituted acridone derivatives. *Open J. Medicinal Chemistry*., **2**, 43-49.

Amareswarao, M.; Babu, Y.R.; Himabindhu, J.; Rajendra, V.V.S. (2016). Synthesis of nitric donating acridone derivatives as cytotoxic agents in cancer. *Der Pharma Chemica*., **8**(4), 391-398.

Avellaneda, A.; Robin, M.; Feure, R.; Perichaud, A.; Galy, J.P. (2002). Spectral assignment and reference data**.** *Mag. Res .Chem*., **40**, 545-548.

Belwal, C.K.; Joshi, K.A. (2012). Synthesis and antifungal activity of some novel thiazolidinone derivatives of 4-(4-oxo-2-phenylthiazolidin-3-yl)benzoic acid. *Int. J. Chem. Tech. Res*., **4**(4), 1758 - 1764.

Denny, W.A.; Atwell, G.J.; Cain, B.F. (1977). Potential anti-tumor agents. 25. Azalogues of the 4'-(9-acridinylamino) methane sulfonanilides. *J. Med .Chem*., **20**(10), 1242.

Drogon, A.S.; Dornor. B.; Thomas, E.; Boguszewsk-Chachulska, M. (2010). Synthesis of new acridone derivatives, inhibitors of NS3 helicase, which efficiently and specifically inhibit sub genomic HCV replication*. J. Med. Chem.,* **53**, 3117-3126.

Ganan, J.M.F. (1973). "Chemistry of Heterocyclic Compounds". Volume 9, John Wiley and Sons, Inc., England, pp. 141-377.

Girohar, A.; Jain, S.; Jain, N.; Girdha, S. (2010). Synthesis and biological studies of novel 9(10H)-acridone derivatives. *Acta Poloniae-Drug Research.,***67**(2), 211-214.

Goa, Ch.; Li, Sh.; Lang, X.; Liu, H.; Liu, F.; Tan, Ch.; Jiang, Y. (2012). Synthesis and evaluation of 10-(3,5-dimethoxy)benzyl-9(10*H*)-acridone derivatives as selective telomeric G-quadruplex DNA ligans. *Tetrahedrone.,***68**, 7920-7925.

Gooldell, J.R.; Madhok, A.A.; Hiasa, H.; Fergusson, D.M. (2006). Synthesis and evaluation of acridine and acridone – based anti – herpes agents with Topo isomerase activity; *Bioorganic and Medicinal Chemistry*., **14**(16), 3467 – 3480.

Gupta, S.K.; Baboo. P. (2015). Synthesis and antimicrobial activity of novel N^{10}–alkyl substituted acridone-9-one derivative. *International. J. Research and Development in Pharmacy and life Science*., **4**(1), 1379-1385.

Hodgemon, D.K.C.; Preger, R.H. (1972). Preparation and properties of the monobromo, nitro, amino and piperdino-10-methylacridones. *Aust. J .Chem*. **25**,191-9.

Huang, C.; Yan, Sh-J.; Zeng, X-h.; Sun, B.; Lan, M-B.; Lin, J. (2015). Synthesis and evaluation of the antitumor activity of polyhalo acridone derivatives. *RSC Advances*., **5**(23),17444-17450.

Jameel, R.K.; Mohammad, S.Kh. (2011). Synthesis of some acridine and acridone derivatives. *The second scientific conference in chemistry, Coll. Science, Mosul* (22-23 November, 2011). 734-746.

Jameel, R.K.; Sheat, A.M. (2014). Synthesis of some new Schiff bases and hydrazones containing benzonaphthyridine / benzonaphthyridine moiety. *Raf. J. Sci*., **25**(3), 56-69.

Kadryavtsera, T.N.; Sysoev, P.I.; Popkov, S.V.; Nazarov, G.V.; Klimova, L.G. (2015). Synthesis and antimicrobial activity of some acridone derivatives bearing 1,3,4-oxadiazole moiety. *Russian Chemical Bulletin, International edition*., **64**(6), 1341-1344.

Kandeel, M.M.; Ali, S.M.; Abdelgawad, M.A.; Abdel-Bakky, M.S.; Mahamed, F.E.A. (2016). Synthesis and cytotoxic activity of acridone substituted with benzimidazole, benzoxazole and benzothiozole. *Der. Pharma. Chemica*., **8**(1), 117-123.

Kannappan, N.; Reddy, B.S.R.; Sen, S.; Nagarajan, R.; Dashute, S. (2009). Synthesis and chemical characterization of quinoline Imine derivatives. *J. Appl. Chem. Res*., **9**,59-68.

Khanaposhtani, M.M.; Mahdavi, M.; Saeedi, M.; Sabourian, R.; Safavi, M.; Khanavi, M.; Foroumade, A.; Shafiee, Kharzadeh, T. (2015). Design, synthesis, biological evaluation, and docking study of cetylcholinesterase inhibitors: new acridone-1,2,4-oxadiazole-1,2,3-triazole hybrids. *Chem. Biol. Drug. De.,* **86**,1425-1432.

Mei, X.; August, A.T.; Wolf, C.; (2006). Regioselective copper-catalyzed amination of o-chlorobenzoic acid: synthesis and solid state structures of N-aryl anthranilic acid derivatives. *J. Org. Chem*., **71**(1),147-149.

Mohammad shabani, Kh.; Aizi, M.; Aghaei, I.; Jahani, R.; Sharfi, Z.; Shamsei, N. (2016). Design, synthesis pharmacological evalution, and docking study of new acridone-based 1,2,4-oxadiazoles as potential anticonvulsant agents. *Eur. J. Med. Chem.,***112**,91-98.

Ugarte, M.M.; Cholewinski, G.; Trzonkowaki, F. (2012). Synthesis and biological activity of novel mycophenolic acid conjugates containing nitro-acridine/ acridone derivatives. *Eur. J. Med. Chem*., **54**,197-201.

Valdes, A.E.C. (2011). Acridine and acridones: old and new structure with antimalarial activity. *The open Med. Chem. J*., **5**, 11-20.

Velingker, V.S.; Dandekar, V.D. (2009). Microwave assisted synthesis and evaluation of anticancer activity of substituted acridone analogues. *Res. J. Pharm. And Tech*., **2**(2), 366 – 370.

Wang, Y.; Gao, D.; Chem, Zh.; Li, Sh.; Gao, Ch.; Cao, D.; Liu, H.; Jiang, Y. (2013). Acridone derivative 8a induces oxidative stress- mediated apoptosis in CCRF-CEM Leukemia cells: Application of metabolomics in mechanistic studies of antitumor agents. *Plos One*., **8**(5), 6372.

Wolf, C.; Mei, X. (2003). Synthesis of conformationally stable 1,8-diarylnaphthalenes: development of new photoiuminescent sensors for ion-selective recognition. *J. Am. Chem. Soc*., **125**, 10651-10658.