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Synthesis and Utility of 6-(β-Phthalimidoethyl) -2-Methyl and/or 2-Phenyl-3, 1-Benzoxazin-4-Ones in Some Heterocyclic Synthesis

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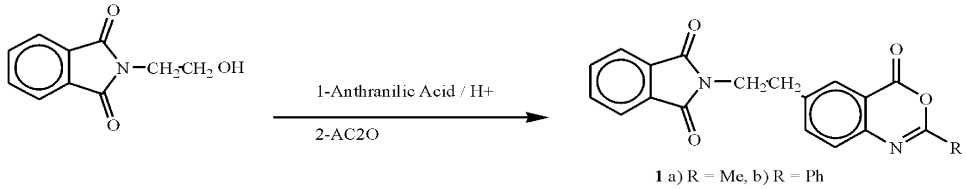
Abstract: The present work deals with synthesis of 3,1-benzoxazinone carrying a new functional group in position-6. The phthalimido group which has been applied as antipsychotic, anti-inflammatory agents and receptors. Hypolipidemic activity for phthalimide derivatives are important in medicinal chemistry and generation of different heterocycles; quinazolinone, triazole and pyrazoloquinazoline derivatives carry β-phthalimidoethyl group, *via* treatment of 3,1-benzoxazinones with nitrogen nucleophiles namely amines, hydrazine, ammonium acetate and hydrazide respectively.

Key words: Phthalimide · Benzoxazine · Quinazoline · Pyrazole · Triazole

INTRODUCTION

4H-3,1-Benzoxazin-4-one have been known for more than a century [1] and compounds possessing this ring system are found in nature [2]. Some derivatives have been shown to possess biological activity. They are potent inactivators of C1r-serine protease [3] as well as inhibitors of human leukocyte elastase [4] and HSV-1 protease [5]. The most popular and versatile route to the 3,1-benzoxazin-4-one moiety relies on anthranilic acid or its derivatives as convenient starting material. The chemistry of the 2-methyl-3,1-benzoxazin-4-one derivatives have been widely studied [6-9], but our knowledge rarely report the chemical behaviour, when the phthalimidoethyl group presents on the benzenic part of molecular [10]. Owing to our interest for access novel heterocyclic compounds with the potential pharmaceutical value i.e. the presence of phthalimidoethyl group in the six position. The authors sought to investigate the behavior of compound **1** towards nitrogen nucleophiles to obtain some interesting heterocyclic compounds containing quinazoline moiety bears at position 6-(β-phthalimidoethyl) which may be enhanced the biological activity [11]of such compounds.



1 a) R = Me, b) R = Ph

DISCUSSION

4H-3,1-Benzoxazin-4-one derivatives bear methyl group at position-2 are called dynamic benzoxazinone as compound **1**a. In the last decades our contributions to solve the synthesis of satisfactorily stable benzoxazinone ring [static benzoxazinone] by replacement saturated substituents by others involving strong conjugation power [12] as **1**b and **2**. The compound **2** can be prepared by condensation of **1**a with various aromatic aldehydes namely benzaldehyde and anisaldehyde.

In continuation of this work on the behavior of dynamic and static benzoxazinone derivatives toward nitrogen nucleophiles namely, amines, hydrazine, formamide and hydrazide to give corresponding 4(3H)-quinazolinone derivatives [13-19] substituted to N-3 can be synthesized to exhibit anticonvulsant property. Modification of the pendant functionalities on a quinazolinone scaffold led to potent antagonist activity [20]. Thus, the present work therefore aimed at synthesizing such compounds. The synthetic routes of compounds are outlined in Fig. 1 and 2.

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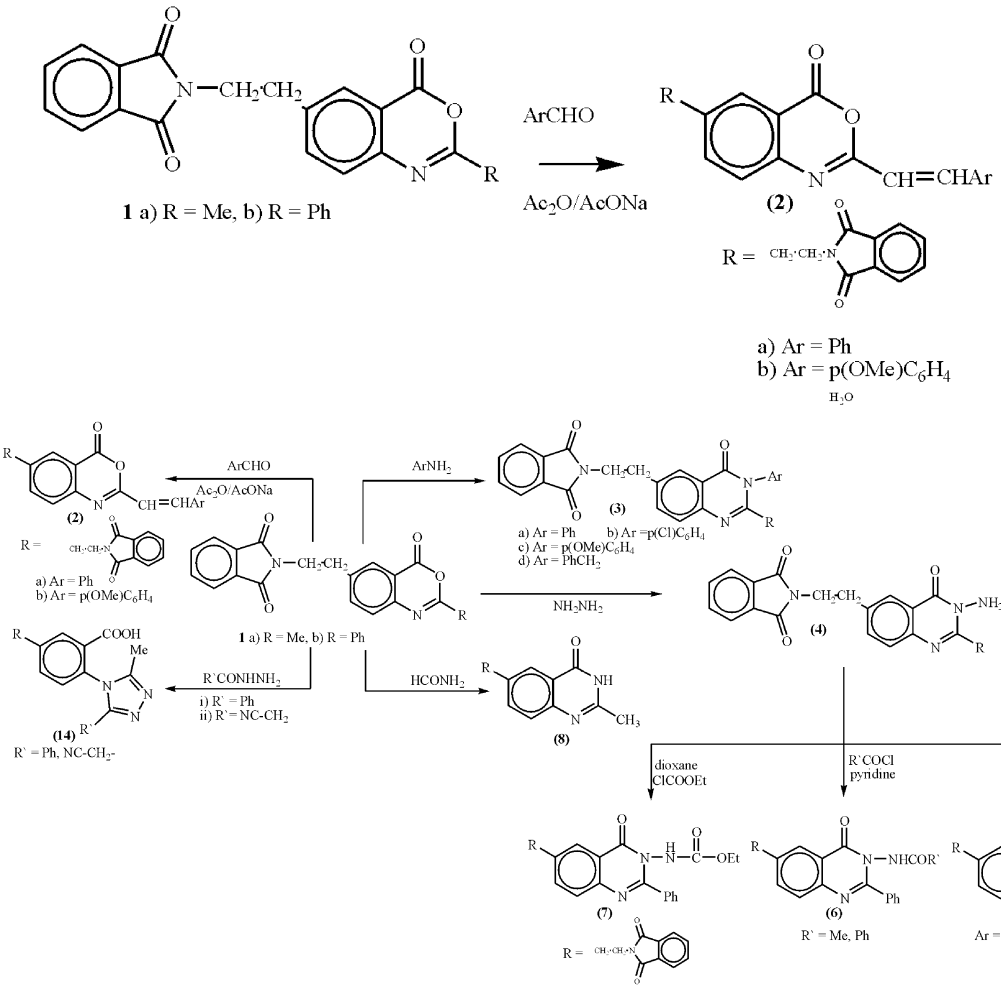


Fig. 1:

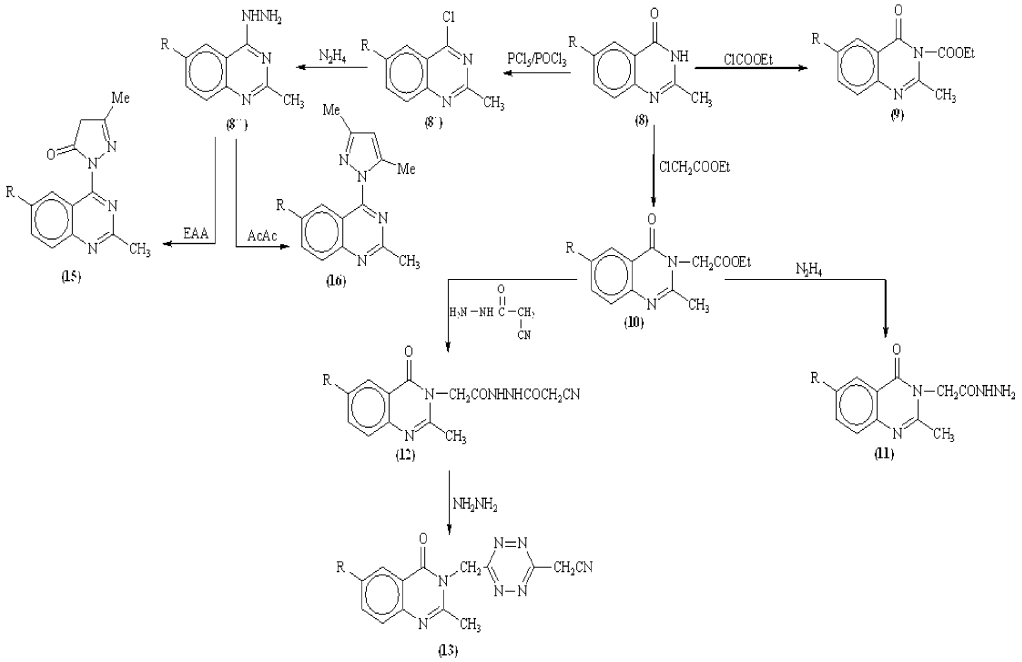
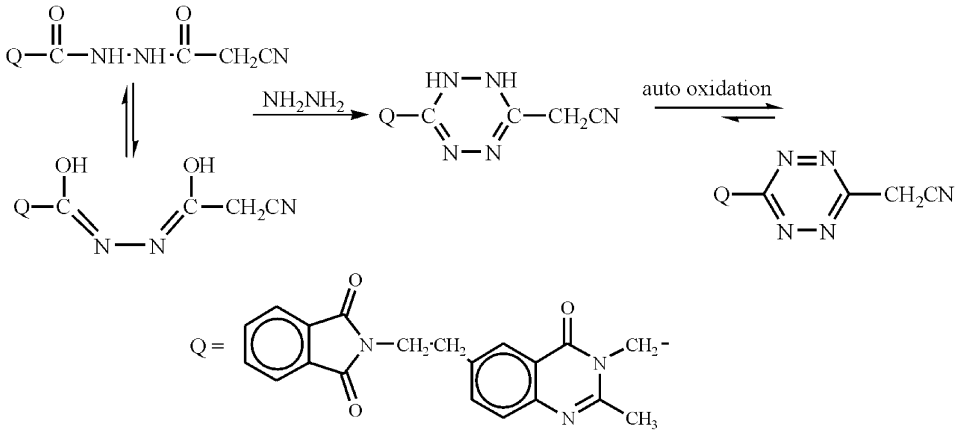


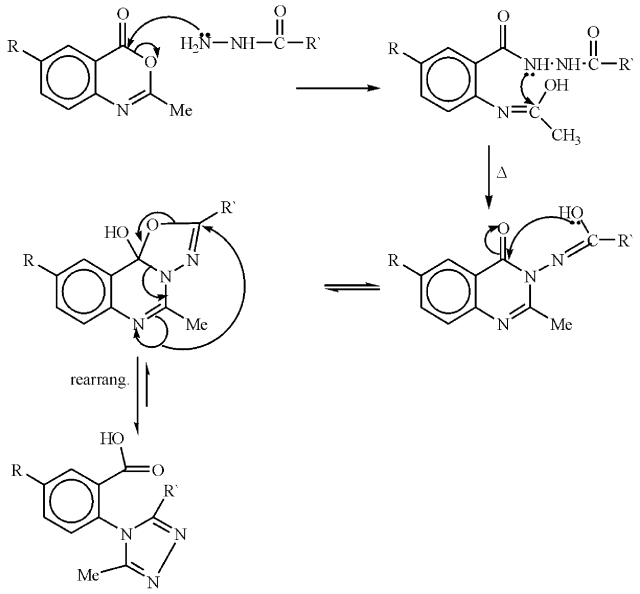
Fig. 2:

Reaction of 2-phenyl-6-(β- phthalimido ethyl)-4H-3,1-benzoxazin-4-one **(1b)** with aromatic amines [21, 22] namely aniline, p-chloroaniline, p-anisidine and benzylamine yielded 3-aryl-6-(β- phthalimido ethyl)quinazolin-4(3H)-ones (3a-d). On the other hand, reaction of **1b** with hydrazine hydrate in boiling dioxane yielded 3-aminoquinazolinone derivative **4**. Reaction of the aminoquinazolinone **4** with aromatic aldehydes, acid chlorides and ethyl chloroformate resulted in the formation of (arylidineimino, acyl and ethoxy carbamido) -4(3H)-quinazolinone derivatives **5**, **6** and **7** respectively.

Reaction of 2-methyl-6-(β- phthalimido ethyl)-4H-3,1-benzoxazin-4-one **(1a)** with formamide yielded 2-methyl-6-(β-phthalimidoethyl)quinazolin-4(3H)-ones **(8)**. A series of quinazolinone derivatives which substituted at N-3 have been synthesized i-via interaction of the quinazolinone **8** with ethyl chloroformate and ethyl chloroacetate afforded **9** and **10** respectively,and ii- reaction of the ester 10 with hydrazine and cyanoacetic hydrazide yielded **11**, **12** incorporating these moieties in N-3 of quinazolinone nucleus might be thought to yield more potent anticonvulsant compound and as substituted moieties are themselves anticonvulsant and substitution at N-3 further, results in protection against convulsions. Thus, the substitution by these moieties may be synergistic [23, 24]. It has been found that reaction of **12** with N_2H_4 in boiling ethanol for 1 hr, it afforded tetrazine derivative **13** to enhance the biological activity more than **12** [25].



Recently, much attention has been focused on 1,2,4-triazole derivatives for their broad-spectrum activities such as fungicidal, herbicidal, insecticidal and anti-inflammatory properties [26-29] take these structural features into consideration, it was thought worth while to synthesize triazole **14** by heterocyclic interconversion of 3,1-benzoxazinone **1a** by treatment of **1a** and benzoic acid hydrazide and/or cyanoacetic hydrazide in boiling acetic acid 8h as outlined.



Reaction of **1a** with hydrazide promoted us by the more observation, that, the combination of two or more heterocyclic and non-heterocyclic systems enhances the biological profile many-fold than its parent nuclei [30, 31]. The authors considered to synthesize 1,2-diazole moiety that combining with (3H)-quinazolin-4-one derivatives. So, the interaction of 4-hydrazino quinazoline derivative 8`` with ethyl acetoacetate and acetyl acetone yielded the pyrazolone and pyrazole derivatives **15** and **16** respectively. Synthesis of the derivatives **15**,**16** may be considered as novel 2,4,6-trisubstituted quinazoline derivatives,their antibacterial and cytotoxic activity against THP-1,HL-60 and A375 cell lines [32].

Experimental: All melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Center, the center publication for research, Cairo, Egypt. By Elementar Viro El Microanalysis IR spectra (KBr) were recorded on infrared spectrometer ST-IR DOMEM Hartman Braun, Model: MBB 157, Canada and H-NMR spectra recorded on a varian 300 MHz (Germany 1999) using TMS as internal standard. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer at 70e.v. homogeneity of all compounds synthesized was checked by TLC. Characterization data of all compounds are given in Table 1 and Spectroscopic data are given in Table 2.

(Methyl-6-(β-Phthalimidoethyl)-3,1-Benzoxazin-4-One (1a): A mixture of 3-(β-phthalimidoethyl) anthranilic acid (0.01 mole) with acetic anhydride (10 ml) was refluxed for 3 h. The reaction mixture was cooled, filter and washed with pet (40-60).

Phenyl-6-(β-Phthalimidoethyl)-3,1-Benzoxazin-4-one (1b): A stirred solution of 3-(β-phthalimidoethyl) anthranilic acid (0.01 mole) in dry pyridine was treated with benzoyl chloride (0.015 mole) dropwise over a period of 30 min. after stirring, reflux 3 h. The reaction mixture was treated with ice/dil HCl. The solid that separated was filtered and recrystallized from proper solvent.

Arylidine Methylene 6-(β-Phthalimidoethyl)-3,1-Benzoxazin-4-One (2): A mixture of compound **1a** (0.01 mole) was reacted with various aromatic aldehydes (0.01 mole) in presence of anhydrous sodium acetate (2 g) in acetic anhydride (15 ml) under reflux 5 h.The reaction mixture was cooled, filtered and washed with H_2O and recrystallized from proper solvent.

Aryl-2-Phenyl-6(β-Phthalimidoethyl)-4(3H)Quinazoline (3a-d): A solution of **1b** (2 gm,0.005 mole) and primary aromatic amine (0.01 mole) namely aniline, p-chloro aniline, p-anisidine and benzyl amine in ethanol (40 ml) was refluxed for 4 hrs. The solid that separated was filtered off and recrystallized from the proper solvent.

Amino, 2-Methyl or 2-Phenyl-6(β-Homothiophthalimido ethyl)-4(3H)-Quinazoline (4): A solution of benzoxazinone **1b** (2 gm,0.005 mole) and hydrazine hydrate (0.5ml,0.01 mole) in dioxane (30 ml) was heated under reflux for 3 hrs. The solid that separated on cooling was filtered off and recrsytallized from the proper solvent.

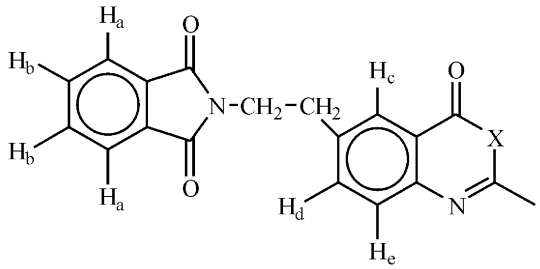
N-Arylidene Imino-2-Methyl/2-Phenyl-6(β-Phthalimido Ethyl)-4(3H)-Quinazoline (5): A mixture of quinazolinone **4** (2 gm,0.005 mole) and aromatic aldehyde (0.005 mole) namely benzaldehyde and anisaldehyde and few drops of piperidine in ethanol (30 ml) was refluxed for 3 hrs. The solid that separated after cooling and concentration was recrystallized from the proper solvent to give **5**.

Acetyl/ Benzoylamino-2-Methyl/ Phenyl-6(β-Phthalimido Ethyl)-4(3H)-Quinazoline (6): A solution of **4** (2 gm,0.005 mole) and acetyl and/or benzoyl chloride (0.015 mole) in dry pyridine (30 ml) was heated under reflux for 3 hrs the reaction mixture was treated with ice/dil HCl, the solid that separated was filtered and crystallized from the proper solvent.

Phenyl-3-Ethyoxy Carbamido -6(β-Phthalimidoethyl)-4(3H)-Quinazoline (7): A solution of **4** (2 gm,0.005 mole) and ethyl chloroformate (1.7 ml,0.015 mole) in dioxane (40 ml) was refluxed for 5 h. The excess solvent was slow evaporated and the solid that separated was filtered off and recrystallized from the proper solvent.

Table 1:

Compd No.	M.P. (°C)	Yield, %	Recryst. Solvent	Mol. F.	Mol. Wt.	Analysis% Cal/Found C	H	N	Cl
1a	120	70	-	$C_{19}H_{14}N_2O_4$	334	68.26	4.19	8.38	-
						68.32	4.21	8.35	
1b	125	60	Benzene	$C_{24}H_{16}N_2O_4$	396	72.72	4.19	7.07	-
						72.73	4.21	7.21	
2a	160	70	Ethanol	$C_{26}H_{18}N_2O_4$	422	73.93	4.26	6.63	-
						73.81	4.28	6.67	
2b	185	70	Ethanol	$C_{27}H_{20}N_2O_5$	452	71.68	4.42	6.19	-
						71.66	4.47	6.15	
3a	175	60	Benzene	$C_{30}H_{21}N_3O_3$	471	76.43	4.45	8.91	-
						76.47	4.47	8.95	
3b	195	65	Benzene-ethanol	$C_{30}H_{20}N_3O_3Cl$	505	71.28	3.96	8.31	6.93
						71.25	4.00	8.29	6.91
3c	190	75	Benzene-ethanol	$C_{31}H_{23}N_3O_4$	501	74.25	4.59	8.38	-
						74.27	4.61	8.41	
3d	160	65	Benzene-ethanol	$C_{31}H_{23}N_3O_3$	485	76.70	4.39	8.66	-
						76.75	4.44	8.69	
4	290	80	Dioxane	$C_{24}H_{18}N_4O_3$	410	70.24	4.39	13.66	-
						70.22	4.36	13.69	
5a	170	70	Ethanol	$C_{31}H_{22}N_4O_3$	498	74.69	4.41	11.24	-
						74.67	4.44	11.27	
5b	185	75	Ethanol	$C_{32}H_{24}N_4O_4$	528	72.72	4.54	10.60	-
						72.75	4.51	10.64	
6a	165	60	Ethanol	$C_{26}H_{20}N_4O_4$	452	69.02	4.42	12.39	-
						69.00	4.45	12.42	
6b	170	60	Ethanol	$C_{31}H_{22}N_4O_4$	514	72.37	4.28	10.90	-
						72.40	4.28	10.92	
7	160	60	Ethanol	$C_{27}H_{22}N_4O_5$	482	67.22	4.56	11.61	-
						67.25	4.55	11.60	
8	220	80	Ethanol	$C_{19}H_{15}N_3O_3$	333	68.47	4.50	12.61	-
						68.49	4.52	12.64	
8`	110	60	Pet 80-100	$C_{19}H_{14}N_3O_2Cl$	351	64.95	4.55	11.96	9.97
						64.92	4.55	11.93	10.00
8``	200	70	Ethanol	$C_{19}H_{16}N_5O_2$	346	65.59	4.62	20.23	-
						65.62	4.65	20.30	
9	155	75	Benzene	$C_{22}H_{19}N_3O_5$	405	65.18	4.69	10.37	-
						65.20	4.66	10.40	
10	125	65	Pet 60-80	$C_{23}H_{21}N_3O_5$	419	65.87	5.00	10.00	-
						65.84	5.00	10.00	
11	180	60	Ethanol	$C_{21}H_{19}N_5O_4$	405	62.22	4.69	17.28	-
						62.17	4.65	17.26	
12	185	55	Ethanol	$C_{23}H_{20}N_6O_4$	444	62.16	4.50	18.91	-
						62.17	4.48	18.89	
13	235	70	Ethanol	$C_{23}H_{18}N_8O_2$	438	63.02	4.11	25.57	-
						63.03	4.12	25.46	
14a	210	70	Ethanol	$C_{26}H_{20}N_4O_4$	452	69.03	4.42	12.39	-
						69.00	4.46	12.42	
14b	240	65	ethanol	$C_{22}H_{17}N_5O_4$	415	63.61	4.09	16.86	-
						63.64	4.12	16.84	
15	284	60	Butanol	$C_{23}H_{19}N_5O_3$	413	66.82	4.60	16.94	-
						66.85	4.63	16.98	
16	260	60	Butanol	$C_{24}H_{21}N_5O_2$	411	70.07	5.10	17.03	-
						70.02	5.13	17.05	



H_e	H_d	H_b	H_c	H_a
7.1 (d, J = 10.5)	7.3 (d,J =10.5 and J=2.4)	7.4 (d, 13.5)	7.6 (d, J = 2.4)	7.8 (d, J = 13.5)

Table 2:

Compd 1	IR (KBr) cm^{-1}	MS m/e	^1H NMR
1a	2954-2890 (C-H), 1774-1710 (C=O of imide), 1740 (C=O of lactone), 1600 (C=C of aromatic ring)	334 $[M]^{+\cdot}$, 188 [$M^{+\cdot}$ -phthimido moiety], 146 [phthalimido radical cation].	2.1 (t, 2H), 2.3 (s, 3H), 3.7 (t, 2H), 7.5 (m, 7H)
1b	3064-2923 (C-H), 1770-1681 (C=O of imide), 1750 (C=O of lactone), 1608 (C=C of aromatic ring)	396 [$M^{+\cdot}$], 222 [$M^{+\cdot}$ - (phthalimido + ethylene moiety)], 146 (phthalimido radical cation).	2.08 (t, 2H), 3.9 (t, 2H), 7.7 (m, 12H)
2a	3085-2878 (C-H), 1777-1700 (C=O of imide), 1750 (C=O of lactone), 1598 (C=C)	420 [$M^{+\cdot}$-H2], 262 [$M^{+\cdot}$ -phthalimido methyl radical], 173 (2-methylbenzoxazinone moiety)	2.08 (t, 2H), 3.9 (t, 2H), 4 (d, 1H), 5.6 (d, 1H), 7.8-8.2 (m, 12H)
2b	3099-2950 (C-H), 1773-1702 (C=O of imide), 1741 (C=O of lactone), 1603 (C=C)	306 [$M^{+\cdot}$- phthalimido], 277 [306 - ethylene], 171 (2-methylbenzox-azinone)	2.08 (t, 2H), 3.2 (s, 3H), 3.9 (t, 2H), 4.1 (d, 1H), 5.5 (d, 1H), 7.9-8.3 (m, 11H)
3a	3059-2926 (C-H), 1790-1700 (C=O of imide), 1741 (C=O of lactam), 1603 (C=C)	469 [$M^{+\cdot}$-H2], 310 [$M^{+\cdot}$ - (phthalimido methyl)], 171 (quinazolinone moiety)	2.08 (t, 2H), 3.9 (t, 2H), 7.2-7.7 (m, 17H)
3b	3022-2903 (C-H), 1779-1701 (C=O of imide), 1682 (C=O of lactam), 1600 (C=C)	505 [$M^{+\cdot}$], 409 [$M^{+\cdot}$ - chlorobenzene], 335 (phthalimidoethyl moiety)	2.08 (t, 2H), 3.9 (t, 2H), 7.2-7.7 (m, 16H)
3c	3073-2927 (C-H), 1770-1700 (C=O of imide), 1678 (C=O of lactam), 1598 (C=C)	499 [$M^{+\cdot}$-H2], 355 [M+ -phthalimido moiety]	2.08 (t, 2H), 3.2 (s, 3H), 3.9 (t, 2H), 7.2-7.7 (m, 16H)
3d	3039-2971 (C-H), 1755-1696 (C=O of imide), 1677 (C=O of lactam), 1599 (C=C)	483 [$M^{+\cdot}$], 311 (M+ -phthalimidoethyl moiety)	2.08 (t, 2H), 3.9 (t, 2H), 4.2 (s, 2H), 7.2-7.7 (m, 17H)
4	3031-3297 (NH), 3022-2912 (C-H), 1772-1711 (C=O of imide), 1667 (C=O of lactam), 1614 (C=C)	410[M+], 250 [M -phthalimido methyl moiety]	2.08 (t, 2H), 3.9 (t, 2H), 7.3-7.8 (m, 12H), 9.6 (s, 2H, disappear by D_2O)
5a	3052-2950 (C-H), 1772-1700 (C=O of imide), 1677 (C=O of lactam), 1595 (C=C)	324 [$M^{+\cdot}$ -phthalimido ethyl], 205 [324 - benzaldehydrazone moiety]	2.08 (t, 2H), 3.9 (t, 2H), 7.3-8.2 (m, 17H), 8.5 (s, 1H, N=CH-Ar)
5b	3037-2927 (C-H), 1779-1703 (C=O of imide), 1672 (C=O of lactam), 1600 (C=C)	526 [$M^{+\cdot}$], 352 [$M^{+\cdot}$ -phthalimido ethyl], 206 [354 - anisaldehydehydrazone]	2.08 (t, 2H), 3.3 (s, 3H), 3.9 (t, 2H), 7.3-8.2 (m, 17H), 8.5 (s, 1H, N=CH-Ar)
6a	3310-3190 (NH), 3030-2890 (C-H), 1790-1697 (C=O of imide), 1700 (C=O of amide),	1685 (C=O of lactam), 1600 (C=C) 450 [$M^{+\cdot}$], 306 [$M^{+\cdot}$ -phthalimido moiety], 236 [306 - ethylene + ketene moieties]	2.08 (t, 2H), 3.3 (s, 3H), 3.4 (t, 2H), 2.8 (s, 3H), 7.3-8.2 (m, 12H), 11.2 (s, 1H, NH), 13.1 (s, 1H, OH)
6b	3442-3270 (NH), 3035-2852 (C-H), 1805-1700 (C=O of imide), 1700 (C=O of lactam), 1690 (C=O of amide), 1586 (C=C)	512 [$M^{+\cdot}$], 393 [$M^{+\cdot}$ - PhN=C=O], 247 [393 -phthalimido ethyl]	2.08 (t, 2H), 2.8 (s, 3H), 3.3 (s, 3H), 3.5 (t, 2H), 7.2-8.5 (m, 17H).
7	3202-3150 (NH), 3079-2988 (C-H), 1760-1690 (C=O of imide), 1733 (C=O of ester), 1652 (C=O of lactam), 1603 (C=C aromatic)	478 [$M^{+\cdot}$], 404 [$M^{+\cdot}$ - (EtOH + CO)], 312 [404 - azopine moiety], 167 [312 -phthalimido]	1.3 (t, 3H), 2.08 (t, 2H), 3.3 (s, 3H), 3.6 (t, 2H), 4.1 (q, 2H), 7.5-8.1 (m, 12H), 12.2 (s, 1H, NH)
8	3199 (NH), 3061 (C-H), 1774-1695 (C=O of imide), 1688 (C=O of lactam), 1602 (C=C of aromatic ring)	331 [$M^{+\cdot}$], 160 [$M^{+\cdot}$ - (phthalimido moiety + ethylene)], 145 (160 - Me)	2.08 (t, 2H), 2.3 (s, 3H), 3.3 (s, 3H), 3.4 (t, 2H), 7.7-8.6 (m, 7H), 12.5 (s, 1H), 13.5 (s, 1H, OH)

Tbale 2: Continued

8`	3050 (C-H), 1779-1702 (C=O of imide), 1612 (C=N, C=C of quinazolone)	369 [$M^{+\cdot}$ + 2], 316 [$M^{+\cdot}$ - CH_3Cl], 127 [(316 - (162 + 28)]	2.08 (t, 2H), 2.3 (s, 3H), 3.3 (s, 3H), 3.6 (t, 2H), 7.2-8.1 (m, 7H)
8``	3330-3158 (NH), 3072-2914 (C-H), 1770-1690 (C=O of imide), 1624 (C=N), 1585 (C=C)	313 [$M^{+\cdot}$ - (N_2 + 3H)], 165 [313 -phthalimide + H_2]	2.08 (t, 2H), 2.41 (s, 3H), 3.3 (s, 3H), 3.5 (t, 2H), 7.1-7.6 (m, 7H), 8.8 (s, 3H, NH-NH_2)
9	3042-2927 (C-H), 1774-1689 (C=O of imide), 1720 (C=O of ester), 1672 (C=O of lactam), 1611(C=C of aromatic rings)	330 [$M^{+\cdot}$ - CO +OEt), 146 [330 - (phthalimido + Me + ethylene)]	1.2 (t, 3H), 2.08 (t, 2H), 3.3 (s, 3H), 3.6 (t, 2H), 4.1 (q, 2H), 2.3 (s, 3H), 7.2-7.9 (m, 7H)
10	3066-2980 (C-H), 1770-1690 (C=O of imide), 1736 (C=O of ester), 1688 (C=O of lactam), 1593 (C=C of aromatic ring)	419 [M^{+}], 332 [$M^{+\cdot}$ - CH_2COOEt], 257 [$M^{+\cdot}$ - 162],	1.2 (t, 3H), 2.08 (t, 2H), 3.1 (s, 3H), 3.8 (t, 2H), 4.1 (q, 2H), 5.1 (s, 2H, N-CH_2-C=O), 7.2-7.9 (m, 7H)
11	3405-3173 (N-H), 3028-2899 (C-H), 1773-1680 (C=O of imide), 1686 (C=O of lactam), 1650 (C=O of hydrazide group), 1588 (C=C of aromatic ring)	349 [$M^{+\cdot}$ - (N_2 + CO)], 190 [349 - phthalimido methyl], 162 [phthalimido methyl moiety]	2.08 (t, 2H), 2.3 (s, 3H), 3.1 (t, 2H), 5.01 (s, 2H, N-CH_2-C=O), 7.3-7.7 (m, 7H), 8.2-8.4 (2 signals 2H, NH_2)
12	3350-3198 (N-H), 3032-2931 (C-H), 2261 (C≡N), 1760-1696 (C=O of imide), 1699 (C=O of lactam), 1654 (C=O of hydrazide group), 1617 (C=N & C=C)	433 [$M^{+\cdot}$ - HCN], 321 [433 - 2 ketene + N_2], 156 [321 - 162]	2.08 (t, 2H), 3.0 (s, 3H), 3.2 (t, 2H), 4.3 (s, 2H), 5.1 (s, 2H, N-CH_2-C=O), 7.2-7.9 (m, 7H), 8.6-8.8 (m, 2H, NH-NH-),
13	3030-2920 (C-H), 2230 (C≡N), 1766-1693 (C=O of imide), 1697 (C=O of lactam), 1620 (C=N of C=C)	434 [M^{+}], 302 [434 - 132], 190[phthalimido ethyl], 132 [cyano methyltetrazino methyl cation]	2.07 (t, 2H), 3.0 (s, 3H), 3.20 (t, 2H), 4.43 (s, 2H, CH_2CN), 5.03 (s, 2H, CH_2CO), 7.1-7.8 (m, 7H).
14a	3030 broad band (O-H), 2973 (C-H), 1773-1690 (C=O of imide), 1681 (C=O of carboxylic), 1616 (C=C of aromatic ring)	406 [468 - CO_2], 234 [406 -phthalimidoethyl radical], 162 [thiophthalimido cation]	2.08 (t, 2H), 2.7 (s, 3H), 3.0 (s, 3H), 3.4 (t, 2H), 7.5-8.1 (m, 12H), 12.2 (s, 1H, COOH)
14b	3050 broad band (COOH), 3010-2960 (C-H), 2225 (CN), 1770 - 1690 (C=O of imide), 1690 (Co of carboxylic)	343 [$M^{+\cdot}$ - (CO_2 + HCN)], 198 [361 -phthalimido radical]	2.08 (t, 2H), 2.7 (s, 3H), 3.0 (s, 3H), 3.4 (t, 2H), 4.2 (s, 2H, NC-CH_2-), 7.5-8.1 (m, 7H)
15	3450 (O-H), 3078 (C-H), 1791-1686 (C=O of imide), 1675 (C=O of pyrazole ring), 1620 (C=N)	429 [M^{+}], 332 [$M^{+\cdot}$ - 97], 142 [quinazolinone cation]	2.08 (t, 2H), 2.4 (s, 6H), 3.0 (s, 3H), 3.7 (t, 2H), 7.4-7.9 (m, 7H), 8.2 (s, 1H, pyrazole), 2.2 (s, 1H, OH)
16	3077 (C-H), 1795-1683 (C=O of imide), 1630 (C=N)	314 [$M^{+\cdot}$ - 95], 146 [phthalimido radical cation], 95 (pyrazole moiety)	2.08 (t, 2H), 2.5 (s, 9H), 3.0 (s, 3H), 3.7 (t, 2H), 7.3-7.7 (m, 7H), 8.2 (s, 1H, pyrazole)

Methyl-6(β-Phthalimido Ethyl)-4(3H)-Quinazoline (8): A solution of **1a** (3.3 gm,0.01 mole) in 20 ml formamide was refluxed for 3 h. The reaction mixture was diluted after cooling with water and the solid that separated was filtered off, dried and recrystallized from the proper solvent.

Methyl-3-Ethoxy Carbonyl -6(β-Phthalimido Ethyl)-4(3H)-Quinazolinone (9): A solution of 8 (1.66 gm, 0.005 mole) and ethyl chloroformate (0.9 ml,0.0075 mole) in dioxane (40 ml) was refluxed for 5 hrs. the excess solvent was slow evaporated and the solid that separated was filtered off and recrystallized from the proper solvent.

Methyl-3-Ethoxy Carbonyl Methyl-6(β-Phthalimido Ethyl)-4(3H)-Quinazoline (10): A solution of **8** (1.66 gm,0.005 mole) and ethyl chloroacetate (1ml,0.0075 mole) and anhydrous potassium carbonate (3 gm,0.02 mole) in dry acetone (30 ml) was refluxed on water bath for 24 hrs. The solvent was removed by distillation and water was added to the reaction mixture. The solid that separated was filtered off and crystallized from the solution solvent.

Methyl-3-N-hydrazino Methyl/ Cyanomethylhydrazino Methyl-4-(β-Phthalimido Ethyl)-4(3H)-Quinazolinone (11,12): A solution of 8 (1.66 gm,0.005 mole) and hydrazine hydrate and/or cyanoacetic hydrazide (0.005

mole) in ethanol (50 ml) was refluxed 5 hrs. The solid that separated was filtered off and recrystallized from proper solvent.

Methyl-4-Chloro-6-(β-Phthalimido Ethyl)-4(3H)-Quinazolinone (8)`: A mixture of **8** (1.66 gm,0.005 mole), PCl_5 (1.5 gm,0.0075 mole) and $POCl_3$ (30 ml) was refluxed on water bath for 1 hr. the excess $POCl_3$ was removed by distillation and water was added to the reaction mixture. The solid that separated was filtered off and crystallized from proper solvent.

Methyl-4-Hydrazino-6-(β-Phthalimidoethyl)-4(3H)-Quinazolinone (8)``:** A solution of **8`** (1.75 gm,0.005 mole) and hydrazine hydrate (0.5 ml,0.01 mole) in ethanol (50 ml) was refluxed 3 hrs. The solid that separated was filtered off and recrsytallized from proper solvent to give **8``.

Methyl-3(6`-Cyanomethyl-1`,2`,4`,5`-Tetrazino-3`-Methyl)-6-(β-Phthalimidoethyl)-4-(3H)-Quinazolinone (13): A solution of **12** (2.2 gm,0.005 mole) with hydrazine hydrate (0.5ml,0.01 mole) in ethanol (30 ml) was heated under reflux for 1 hr. The solid that separated was filtered off, dried and crystallized from the proper solvent.

(3-Methy-5-Phenyl/Cyanomethyl1,2,4triazolo-4-yl)5-Phthalimidoethyl Benzoic Acid 14: A solution of **1a** with benzoic and/or cyanoacetic hydrazide (0.01 mole) in acetic acid (50 ml) was heated under reflux 8 hrs. after cooling the reaction mixture was diluted with H_2O. The solid that separated was filtered off, dried and crystallized from the proper solvent.

Methyl-4-(3-Methylpyrazol-5-on-1-yl)-6-(β-Phthalimidoethyl)-4-(3H)-Quinazolinone 15: A solution of **8``** (0.01 mole) with ethylacetoacetate (0.01 mole) in ethanol (50 ml) was heated under reflux for 8 h. The solid that separated was filtered off, dried and crystallized from the proper solvent.

Methyl-4-(3,5-Dimethylpyrazolo-1-yl)-6-(β-Phthalimidoethyl)-4(3H)-Quinazolinone 16: A solution of **8``** (0.01 mole) with acetylacetone (0.01 mole) in ethanol (50 ml) was heated under reflux for 8 h. The solid that separated was filtered off, dried and crystallized from the proper solvent.

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