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Synthesis and anti-diabetic activity of some 3-methylquinazolin-4(3*H*)-one derivatives

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Abstract : The reaction of 2-*N*-azidoacetylarylaminomethyl-3-methylquinazolin-4(3*H*)-one (**1**) with TEP, and the anti-diabetic activity of the resulting diethyl 2-(((3-methyl-4-oxo-3, 4-dihydroquinazolin-2-yl)methyl)(aryl)amino)-2-oxoethylphosphoramidate (**2**) are reported.
Keywords: Quinazolin-4(3*H*)-one, Azide, Triethyl phosphate (TEP), Anti-diabetic.

1. Introduction

2-Heteryl and heteroalkyl quinazolin-4(3*H*)-ones exhibited a wide range of pharmacological properties such as antimicrobial[1,2],antibacterial[3- 6]cytotoxicity [7], analgesic [8,9] , antifungal[3,10,11] , anti-inflammatory[12-14], poly(ADP-ribose)polymerase-1 inhibitors[15], anticonvulsant[16], and hypolipidemic agents.[17] Earlier, we have published synthesis and biological activity of 2-heteryl- quinazolin-4(3*H*)-one.[18-23] As part of a general scheme to synthesize new 2-heteryl quinazolinones, we attempted to prepare 2-imidazolidinonylquinazolin-4(3*H*)-ones (**3**) starting from 2-chloromethyl-3-methylquinazolin-4(3*H*)-one (Fig.1). Reflux of the intermediate azide, 2-*N*-azidoacetylarylaminomethyl-3-methylquinazolin-4(3*H*)-one (**1**), in decalin, for example, yielded surprisingly 2, 3-dimethylquinazolin-4(3*H*)-one (**4**), whereas triflic acid in methylene dichloride caused deacylation to form 2-arylaminomethyl-3-methylquinazolin-4(3*H*)-one (**5**).[20] However, reacting **1** with KOH in dioxane yielded imidozolidinonylquinazolin-4(3*H*)-ones, but in low yields (vide hplc). Triethyl phosphate (TEP) is known to generate nitrene from nitro and azide groups and is now used to prepare **3** from **1** in good yield.[24, 25]

2. Experimental Protocol

2.1. Materials and methods

Experimental Section

All melting points mentioned in this chapter were determined in capillaries using Polman digital melting point apparatus (Model No. Mp96) and reported in degree centigrade. Ultraviolet spectra were recorded in methanol on Shimadzu 1520 ultraviolet-visible spectrophotometer and the absorption maxima were presented in nm along absorption. Infrared spectra were recorded in KBr pellets on Shimadzu 435 instrument. The absorptions were quoted in cm^{-1}. Proton magnetic resonance spectra were recorded on Varian Gemini (200 MHz) spectrophotometer with TMS as internal standard. Chemical shift values were given in δ scale. The solvent in which the NMR spectra were recorded is indicated at the appropriate places. Mass spectra were recorded on VG-micromass 70-70H instrument with direct inlet probe. The pharmacological evaluations of the products were carried out at Department of Zoology, Osmania University. Hyderabad and Novo Nordisk. Female diabetic ob/ob mice 10-11 weeks of age (Umea) and their lean control were maintained under a 12: 12

light-dark cycle with free access to water and food. All the mice were weighed and bled via the tail vein for blood glucose values. Body weight was also measured regularly.

2.2. Typical procedure for synthesis of diethyl 2-(((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)(aryl)amino)-2-oxoethylphosphoramidate (**2**, **a-e**).

The 2-*N*-azidoacetylarylaminomethyl-3-methylquinazolin-4(3*H*)-one (**1 a-e**, 1 mmol) was suspended in triethyl phosphate (5 mL) and refluxed under nitrogen atmosphere. After a short period of heating, gas evolution was noted; heating was continued until gas evolution ceased (2h). The remaining solid, characterized as diethyl 2-(((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)(aryl)amino)-2-oxoethylphosphoramidate (**2**), was filtered and purified over column of neutral alumina using benzene-ethyl acetate (7:3) as eluent. The same compound was also obtained at room temperature after 24h. The tentative mechanism for the formation of **2** from **1** is shown in Scheme **2.**

2.2.1. Diethyl 2-(((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)(phenyl)amino)-2-oxoethylphosphoramidate (2a)

Yield 88%. mp 153-155 ^{o}C. UV(MeOH, λ_{max}): 305 (0.075), 268 (0.134), 224 (0.550); IR(KBr υ_{max}/cm^{-1}):3278, 3056, 2979, 2931, 1679 (br), 1606, 1475, 1417, 1385, 1314, 1234, 1131, 1060, 1034, 960, 901, 783, 697, 641;^{1}H NMR(200 MHz, $CDCl_3$) δ (ppm): 1.3 (t, 6H, J = 7.2 Hz, 2 x CH_3), 3.55 (d, 2H, $J_{H,P}$ = 8.0 Hz, CO-CH_2), 3.6 (s, 3H, N-CH_3), 4.0 (ABm, 4H, 2 x OCH_2), 5.0 (s, 2H, N-CH_2), 7.4 - 7.8 (m, 8H, Ar-H), 8.25 (d, 1H, J = 7.2 Hz, peri proton); EIMS(20 eV): m/z (rel.int.,%) 458 (M+ , 1.5), 413 (1.5), 292 (100), 264 (31), 174 (16), 166 (13), 138 (6), 132 (10), 110 (15), 77 (5).

2.2.2. Diethyl 2-(((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)(4-methylphenyl) amino)-2-oxoethyl phosphoramidate (2b)

Yield 67%. mp 177-180 ^{o}C. UV(MeOH, λ_{max}): 305 (0.116), 268 (0.202) and 224 (0.879); IR(KBr υ_{max}/cm^{-1}): 3276, 3035, 2981, 1671 (br), 1607, 1543, 1511, 1475, 1337, 1312, 1235, 1131, 1055, 1031, 960, 901, 785, 695, 641; ^{1}H NMR(200 MHz, $CDCl_3$) δ (ppm): 1.25 (t, 6H, J = 7.2 Hz, 2 x CH_3), 2.35 (s, 3H, Ar-CH_3), 3.55 (d, 2H, $J_{H,P}$= 8.2 Hz, CO-CH_2), 3.6 (s, 3H, N-CH_3), 4.0 (ABm, 4H, 2 x OCH_2), 4.95 (s, 2H, N-CH_2), 7.1 - 7.75 (m, 7H, Ar-H), 8.25 (d, 1H, J = 8.4 Hz, peri proton); ^{13}C NMR($CDCl_3$, 50 MHz): 170.13, 169.94, 162.16, 150.88, 146.78, 139.17, 137.73, 133.96, 130.57, 128.06, 127.2, 126.72, 120.4, 62.45, 62.35, 52.09, 43.41, 29.51, 20.99, 16.16, 16.02; EIMS(20 eV): m/z (rel.int.,%) 472 (M+ , 1.5), 427 (1.5), 306 (100), 278 (20), 174 (8), 120 (8).

2.2.3. Diethyl 2-(((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)(4-methoxyphenyl) amino)-2-oxoethylphosphoramidate (2c)

Yield 61%. mp 229-230 ^{o}C. UV(MeOH, λ_{max}): 305 (0.071), 268 (0.138) and 225 (0.609); IR(KBr υ_{max}/cm^{-1}): 3263, 2956, 1673 (br), 1607, 1511, 1386, 1313, 1234, 1130; ^{1}H NMR(200 MHz, $CDCl_3$) δ (ppm): 1.3 (t, 6H, J = 7.2 Hz, 2 x CH_3), 3.55 (d, 2H, $J_{H,P}$ = 8.3 Hz, CO-CH_2), 3.6 (s, 3H, N-CH_3), 3.8 (s, 3H, OCH_3), 4.0 (ABm, 4H, 2 x OCH_2), 4.95 (s, 2H, N-CH_2), 6.8 - 7.8 (m, 7H, Ar-H), 8.25 (d, 1H, J = 7.9 Hz, peri proton).

2.2.4. Diethyl 2-(((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)(4-ethylphenyl) amino)- 2-oxoethyl phosphoramidate (2d)

Yield 70%. mp 140-141 ^{o}C. UV(MeOH, λ_{max}): 305 (0.091), 268 (0.161) and 224 (0.737); IR(KBr υ_{max}/cm^{-1}): 3268, 2967, 2927, 1679 (br), 1607, 1511, 1474, 1417, 1386, 1311, 1234, 1131, 1060, 1032, 962, 783, 695, 641, 498; ^{1}H NMR(200 MHz, $CDCl_3$) δ (ppm): 1.2 (t, 3H, J = 7.2 Hz, CH_3), 1.25 (t, 6H, J = 7.2 Hz, 2 x CH_3), 2.65 (q, 2H, J = 7.2 Hz, CH_2), 3.55 (d, 2H, $J_{H,P}$ = 8.0 Hz, $COCH_2$), 3.6 (s, 3H, N-CH_3), 4.0 (ABm, 4H, 2 x OCH_2), 4.95 (s, 2H, N-CH_2), 7.1 - 7.7 (m, 7H, Ar- H), 8.2 (d, 1H, J = 8.5 Hz, peri proton); EIMS(20 eV): m/z (rel.int.,%) 486 (M+ , 1.5), 441 (1.5), 320 (100), 292 (22), 174 (12), 134 (10), 110 (10)

2.2.5. Diethyl 2-(((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)(4-chlorophenyl) amino)-2-oxoethyl phosphoramidate (2e)

Yield 80%. mp 10-111 ^{o}C. UV(MeOH, λ_{max}): 306 (0.079), 267 (0.143) and 225 (0.701); IR(KBr υ_{max}/cm^{-1}): 3282, 3062, 2978, 2931, 1672 (br), 1607, 1491, 1383, 1313, 1234, 1131, 1031, 961, 840, 781, 696, 642, 591; ^{1}H NMR(200 MHz, $CDCl_3$) δ (ppm): 1.3 (t, 6H, J = 7.2 Hz, 2 x CH_3), 3.55 (d, 2H, $J_{H,P}$ = 8.1 Hz, CO-

CH_2), 3.6 (s, 3H, N-CH_3), 4.0 (ABm, 4H, 2 x OCH_2), 4.95 (s, 2H, N-CH_2), 7.3 - 7.7 (m, 7H, Ar-H), 8.2 (d, 1H, *J* = 7.9 Hz, peri proton).

2.3. Biological activity

The pharmacological evaluations of the products were carried out at Department of Zoology, Osmania University. Hyderabad and Novo nordisk. Female diabetic ob/ob mice 10-11 weeks of age (Umea) and their lean control were maintained under a 12: 12 light-dark cycle with free access to water and food. All the mice were weighed and bled via the tail vein for blood glucose values. Body weight was also measured regularly.

2.3.1: 14C-Glucose incorporation into isolated rat soleus muscle.

Muscle is incubated for 120 min with 0.2 nM insulin ± compound. 14C glucose is present for the last 60 min. 14C glucose incorporation into glycogen is measured. The results are reported in Table-1 and Table-2. Compound **2e** at 1µM or 10 µM did not significantly change the insulin stimulated glucose incorporation into glycogen in isolated rat soleus muscle.

2.3.2: 2-Deoxy-Glucose transport in incubated rat skeletal muscle (soleus)

Compound **2e** (10µm and 100 µm) tested with 0.1nM insulin present. Incubation for 2h, 2-deoxy-14C-glucose added for the last 20 min., thereafter the 2-deoxy-14C-glucose uptake is measured. The results are reported in Table-3 and Table-4. No effect of compound **2e** on glucose uptake at 10µM. inhibitory at 100µM.

2.3.3: Lipogenesis in primary mouse adipocytes

Lipogenesis performed in primary mouse adipocytes, estimated by measuring extractable 3-H lipids produced from 3-H-glucose. The results are reported in Table-5 and Fig-2. A dose dependent inhibition of insulin stimulated lipogenesis was observed (i.e. insulin sensitivity was decreased).

2.3.4: Hepatic effects

Using the following protocols:

A) Glycogen phosphorylase in a (GPa) obtained from pig liver was measured in thedirection of glycogen degradation.
B) Hepatocytes (Rat) were cultured under normal conditions for 48h where after the culture medium was changed to a Gluco-buffer without glucose and supplemented with 3mM glycerol and 0, 25, or 50 µM test compound. Cells were further incubated for 2 h and subsequently the amount of glucose in the Gluco-buffer was meseared.
C) Hepatocytes (Rat) were cultured under normal conditions for 48h where after the culture medium was changed the same culture medium further supplemented with glucose and insulin to a final concentration of 15 µM and 10 nM, respectively, and cells were further incubated for 24h in order to build up glycogen. After 24h the medium was changed to a gluco-buffer without glucose and supplemented with 2 nM glucagon in order to stimulate glycogen breakdown and 0, 25, 50 µM test compound. Cells were then incubated for 2h and subsequently the amount of glucose in the Gluco-buffer was measured.

Protocol B) is a measure of gluconeogenesis and protocol C) is a measure of glycogenolysis.

Results protocol A)

Compound (µM)	**%**
control	100
1	98
10	97
100	103

Results protocol B)

Compound (µM)	**%**
control	100
25	112
50	123

Results Protocol C)

Compound (µM)	**%**
control	100
25	99
50	100

The tested compound was not found to inhibit glycogen phosphorylase using semi-purified pig liver GPa or gluconeogenesis or glycogenolysis measured in cultured rat hepatocytes.

2.3.5: Insulin release from Mouse Pancreatic Islets

In brief, isolated mouse islets were incubated for 1h in 2.5 or 10mM glucose with our without **2e.** The sample was analyzed for insulin by an insulin ELISA. The results are reported in Table-6 and are expressed as insulin produced / minute/islet. A significant increase in insulin release was seen at 100µM with 2.5 mM glucose in medium.

2.3.6: Acute effect on bloodglucose in ob/ob mice.

Design:

Female, diabetic ob/ob mice (Umea), 10-11 weeks of age (n=5-6)

One single i.p dose (90mg/kg) to unfasted animals (food available during experiment).

Blood glucose measured from the tip of the tail in conscious animals at 0.5, 0, 1, 2, 4, 6, and 8 hours after dosing (Fig-3).

T-test Two sample		Unequal variance
P BG (2e) <BG (Vehicle)	=	0.0289(4 hours) *
P BG (2e) <BG (Vehicle)	=	0.0004(6 hours) ***
P BG (2e) <BG (Vehicle)	=	0.0004(8 hours) ***

One single i.p dose (90 mg/kg) to unfasted animals (food available during experiment) was given. Blood glucose was measured from the tip of tail in conscious animals at 0.5, 0.0, 1, 2, 4, 6 and 8 hours after dosing. At the same time, the lean mice were also treated with vehicle (CMC, carboxy methyl cellulose) and compound **2e** with vehicle (1% CMC). The mice **1** injected with 1.35 mg (90 mg/kg), mice **2** is with 2.7 mg(180mg/kg) , mice **3** with 4.05mg (270 mg/kg) and mice **4** without sample (only DMSO). There was a significant blood glucose lowering effect on the compound after 4, 6, and 8 hours post dosing.

3. Results and Discussion

3.1. Chemistry

2-*N*-Azidoacetyl-(4-methylphenyl)aminomethyl-3-methylquinazolin-4(3*H*)-one (**1b**) was heated in TEP under nitrogen atmosphere. After a short period of heating, gas evolution was noted; heating was continued for 2h. The solid left was purified over a column of neutral alumina (~150 mesh) using benzene-ethyl acetate (7:3) as eluent. The same product was obtained in 85% yield when the reaction was carried out at room temperature, but it required 24h for the completion of the reaction. On silica plate, this compound (m.p.177-180^{0}C) gave a white spot on spraying with H_2SO_4 and heating, characteristic of phosphorous containing molecules.

The ultraviolet spectrum of the above compound **2b** showed the λmax at 305, 268 and 224 nm was similar to **1b** (305,268 and 224) (Reddy et al., 2003). The infrared spectrum (KBr) showed sharp NH peak (3276 cm-1) and broad carbonyl peak (1671 cm-1). The ^{1}H NMR spectrum ($CDCl_3$) suggested the presence of quinazolinone and 4-methylphenyl moieties (δ 2.35 (s, 3H, Ar-CH_3), 3.6 (s, 3H, N-CH_3), 7.1 – 7.75 (m, 7H, aromatic) and 8.25 (d, 1H, peri proton)). Surprisingly, the spectrum also indicated the presence of two ethoxy groups at δ 1.25 (t, 6H, 2 x CH_3) and δ 4 (ABm, 4H, 2 x OCH_2). The other peaks are due to CH_2CO (δ 3.55, d, $J_{H,P}$=8.2 Hz, 2H) and NCH_2 (δ 4.95, s, 2H) respectively. The ^{13}C NMR spectrum ($CDCl_3$) further corroborated the presence of the above structural features. Two carbonyl carbons appeared at δ 169.94 and 170.13. Signals at

δ 62.45, 62.35 and 16.16, 16.02 are due to the ethoxy groups. Methylene carbons corresponding to CH_2N and CH_2CO appeared at δ 52.09 and 43.41 respectively. In the EI mass spectrum (20 eV), the highest ion peak was at m/z 472 corresponding to the molecular formula $C_{23}H_{29}N_4O_5P$. The molecular ion suffered the loss of ethoxy group under electron impact, resulting in the ion at m/z 427. The appearance of a strong doublet peak at 1030–1065 cm^{-1} in the IR spectrum confirms the presence of C-O-P (aliphatic) bond. [26] Based on all these spectral data, the compound was assigned as diethyl 2-(((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)(4-methylphenyl)amino)-2-oxoethylphosphoramidate (**2b**) structure. The mechanism for the formation of compound **2** from **1** is possible by reaction of compound **1**with TEP followed by the elimination of ethylene moiety (Scheme **1**).

Four other azides (**1a**, **1c**, **1d** & **1e**) reacted similarly with TEP to yield the corresponding diethoxyphosphorylamino derivatives **2** characterized by analogy and spectral data (Scheme **2**).

3.2. Biological evaluations

During the structure elucidation of these compounds, the thorough literature study revealed that this class of compounds exhibits hypolipidemic activity.[17] As a representative case, one of the compound **2e** synthesized was tested for anti-diabetic activity in the following experiments.

1. 14C-Glucose incorporation into isolated rat soleus muscle,
2. 2-Deoxy-Glucose transport in incubated rat skeletal muscle (soleus),
3. Lipogenesis in primary mouse adipocytes ,
4. Hepatic effects
5. Insulin release from Mouse Pancreatic Islets
6. Acute effect on bloodglucose in ob/ob mice.

It has been observed that the compound **2e** is shown a significant increase in insulin release from mouse pancreatic islets at 100 µM with 2.5 mM glucose in medium and acute blood glucose lowering effect in ob/ob mice after 4, 6, and 8 hours post dosing. The compound **2e** has not exhibited significant activity for 14C-glucose incorporation into isolated rat soleus muscle, 2-deoxy-glucose transport in incubated rat skeletal muscle (soleus), lipogenesis in primary mouse adipocytes and hepatic effects.

4. Conclusion

A convenient method for the synthesis of novel diethyl 2-(((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)(aryl)amino)-2-oxoethylphosphoramidate (**2**) starting from 2-*N*-azidoacetylarylaminomethyl-3-methylquinazolin-4(3*H*)-one (**1**) was developed. The newly synthesized compounds exhibit remarkable acute blood glucose lowering effect in ob/ob mice after 4, 6, and 8 hours post dosing at low concentrations. The results of the present investigation indicate the importance of these novel compounds as potential lead candidates.

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References

1 Achaiah, G., Jayamma, Y and Reddy, V.M., Synthesis and biological evaluation of 2-[3-aryl-4(3*H*)-quinazolinon-2yl]pyrrolino[5,4-*b*]2,3-dihydro-4*H*-[1]-benzopyran-4-ones. Ind. J. Heterocycl. Chem., 1991, 1, 39-42.

2 Shiba, S.A., El-Khamry, A.A., Shaban, M.E., Atia, K.S., 1997. Synthesis and antimicrobial activity of some bis(quinazoline) derivatives. Pharmazie. 52, 189-194.

3 Seshavataram, S.K.V and Rao, N.V.S., Synthesis of 7-chloro-2-methyl- and 2-(2-furyl)-3-aryl-4-quinazolones, Proc. Ind. Acad. Sci. Sect A., 1977, 85, 81-89.

4 Shukla, J.S and Fadayan, M., Synthesis of 2-methyl/phenyl-3-[4-(substituted-benzylidene amino)phenyl]-6- and -8-disubstituted-1,3-quinazolin-4-ones as potential anthelmintic agents. Asian J. Chem., 1989, 1, 208-213.

5 El-Deen, I.M., Mohamed, S.M., Ismail, M.M.; Abded, M.M., Synthesis and chemistry of 2-(5-mercapto-4-phenyl-1,2,4-triazol-3-yl)-3-phenyl-4(3*H*)-quinazolone. An. Quim., 1993, 89, 621-624.

6 Kamel, M.M., Ismail, M.M., Abd, E.B., Moneib, N.A., Synthesis of certain quinazolinone derivatives of pharmaceutical interest. Egypt J. Pharm. Sci., 1991, 32, 191-204.

7 Hee-Kyung, R., Ji Hye, Yoo., Eunyoung, L., Young, J.K., Hang-Rhan, S., Yun-Sil, L., Hea-Young, P.C., Synthesis and cytotoxicity of 2-phenylquinazolin-4(3*H*)-one derivatives. Eur. J. Med. Chem., 2011, 46, 3900-3908.

8 Plescia, S., Daidone, G., Ceraulo, L., Bajardi, M.L., Reina, R.A., 3-Isoxazolyl-substituted 4(3*H*)-quinazolinones of pharmaceutical interest. Farmaco. Ed. Sci., 1984, 39, 120-124.

9 Nikolova, M., Stefanova, D., Nikolova, R., Ilarinov, I., Ivanov, K., Characteristics of the analgesic effect of a quinazolone derivative. Farmasiya. 1977, 27, 53-59.

10 Mittra, P., Mittra, A.S., Synthesis of quinazolone and benzimidazole and their derivatives as potential fungicides. Acta Ciencia Indica Chem., 1983, 9, 109-114.

11 Mahmoud, A.M., El-Sherief, H.A.H., El-Naggar, G.M., Abdel-Rahman, A.E., Synthesis of 5-mercapto-1,2,4-triazole derivatives containing 4(3*H*)-quinazolone nucleus. Ind. J. Chem., 1983, 22B, 491-493.

12 Farghaly, A.M., Chaaban, I., Khalil, M.A., Behkit, A.A., Synthesis of novel pyrazole and pyrazoline derivatives of 4(3*H*)-quinazolinone. Arch. Pharm., 1990, 323, 311-315.

13 Singh, I.P., Saxena, A.K., Sinha, J.N., Bhargava, K.P., Shankar, K., Synthesis and antiinflammatory activity of 2-substituted-phenethyl-3-substituted-phenyl-4(3*H*)-quinazolinones. Ind. J. Chem., 1984., 23B, 592-594.

14 El-Faky, S.A., Abd el-Samii, Z.K., Synthesis and antiinflammatory properties of some novel thiazolidinones and imidazolidinones derived from 4-(3-phenyl-4(3*H*)-quinazolinon-2-yl)-3-thiosemicarbazone. Pharmazie., 1995, 50, 341-343.

15 Tuong, V.T.L., Jee, H.S., Nakjeong, K., Hyun-Ju, P., In silico identification of poly(ADP-ribose)polymerase-1 inhibitors and their chemosensitizing effects against cisplatin-resistant human gastric cancer cells. Bioorg. Med. Chem. Lett., 2013, 23, 2642-2646.

16 Abdel-Hamide, S.G., Ghorab, M.M., Badary, D.A., Synthesis and radiation stability of certain 1,3,4-oxadiazole derivatives of expected anticonvulsant activity. Egypt J. Biotechnol., 1997, 1, 36-45.

17 Yasuhisa, K., Yasuhide, I., Kazuhiko, T., Shizuo, N., Kazushi, N., Hiroki, Y., Yoshihikko, T., Synthesis and Hypolipidemic Activities of Novel 2-[4-[(diethoxyphosphoryl) methyl]phenyl] quinazolines and 4(3*H*)-Quinazolinones. J. Med. Chem., 1996, 39, 1433-1437.

18 P S N Reddy, T.Vasantha & Ch. Naga Raju, 4-Heteryl-β-lactams : A facile synthesis of 1-aryl-4-[isopropylideneamino/ methyl-4(3H)oxoquinazolin-2-yl]azetidin-2-ones, Ind. J. Chem., 1999, 38B(1), 40-44.

19 P S N Reddy, P Pratap Reddy & T Vasantha. Bisazaheterocycles Part-VII: Synthesis of novel bisquinazolinonyl β-lactams, Ind. J. Chem., 2002, 41B(9), 1946-1949.

20 P S N Reddy, P Pratap Reddy & T Vasantha. Synthesis of 2-quinazolinonyl imidazolidinones, Ind. J. Chem., 2003, 42B(2), 393-396.

21 P S N Reddy, P Pratap Reddy & T Vasantha. A review on 2-heteryl and heteroalkyl 4(3H)-quinazolinones, Heterocycles, 2003, 60(1), 183-226.

22 P S N Reddy, P Pratap Reddy & T Vasantha. Bisazaheterocycles Part VIII: A new synthesis of 2,2'-bisquinazolinones, Ind. J. Chem., 2002, 41B(9), 1950-1952.

23 Vasantha Mittapelli, V.D Reddy, P S N Reddy, Antibacterial, antifungal and antifeedant activity of quinazolinonyl-β-lactams/ quinazolinones and bis(quinazolinonyl-β-lactams), Rasa. J. Chem., 2010, 3(4), 635-640.

24 Polts, K.T., Marshall, J.L., Thiazolo[3,4-*b*]indazole, a ring-fused tetravalent sulfur thiazole system. J. Org. Chem., 1976, 41, 129-133.

25 Cadogan, J.I.G., Machie, R.K., Todd, M., The reaction of triethyl phosphite with o-dinitrobenzene: evidence for aromatic substitution by tervalent phosphorus. J. Chem. Comm., 1966, 491-492.

26 Silvestein, R.M., Clayton, B.G., Terence, C.M., Spectrometric identification of organic compounds., 1991, 5, 164.

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